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2.0	18-Feb-2016	Sean McCandless	Version control introduced

Microwave tissue ablation for primary and secondary liver cancer

September 2016

MSAC application no. 1402

Assessment report

CONTENTS

TABLES

BOXES

FIGURES

EXECUTIVE SUMMARY

Main issues for Medical Services Advisory Committee consideration

- The clinical claims for the superiority of microwave tissue ablation (MTA) over radiofrequency ablation (RFA) made in the application are not supported by the evidence.

- There is very little randomised controlled trial evidence for this intervention.

- Much of the evidence included for this intervention uses historical controls; that is, institutions went from using RFA to using MTA, and then compared the experience of the MTA patients with the experience of earlier patients. This is likely to have important ramifications for the effectiveness of the intervention, as many other aspects of the treatment may also have changed in that time, such as chemotherapy, imaging, patient selection for ablation and surgery, and the equipment used to deliver the ablation.

- Selection bias is also highly likely in most of the populations included in the evidence base, as most studies simply included patients seen in their institutions, and there was little discussion about who was excluded from analyses or how patients were selected for ablation. Moreover, in most studies, there was a lack of information relevant to prognosis, for example time since diagnosis, and these factors are likely to confound the results.

- There does seem to be some evidence that MTA works better than RFA in more severe cases of cancer; however, given the problems with historical controls, the superior effectiveness may actually be due to improvements in other treatments, or indeed in patient selection for the treatment.

- In patients with liver metastases, most of the identified evidence was excluded because patients underwent concomitant resection (meaning they were not 'unresectable' as described in the 'Population' component of the PICO criteria). It is likely that patients in this group, who have more complex disease, undergo a range of treatments, and finding evidence for just one of them in isolation will be difficult.

- Despite the claims that MTA has quicker ablation time and fewer required sessions, there was little evidence available to support these claims.

Microwave tissue ablation for primary and secondary liver cancer

This contracted assessment examines the evidence to support the listing of microwave tissue ablation (MTA) on the Medicare Benefits Schedule (MBS). The service would be used for the treatment of unresectable primary and secondary liver tumours. There are three target populations:

1) Patients with unresectable primary liver lesions in whom MTA is used with curative intent.

2) Patients with unresectable secondary liver lesions, without extrahepatic spread, in whom MTA is used with curative intent.

3) Patients with unresectable neuroendocrine liver metastases, with or without extrahepatic spread, who are refractory to somatostatin analogue therapy, in whom MTA is used for palliative treatment of secretory syndromes.

The Protocol Advisory Sub-Committee (PASC) of the Medical Services Advisory Committee (MSAC) also asked that the assessment consider the method of delivery of the ablation: percutaneous, laparoscopic or open surgical.

ALIGNMENT WITH AGREED PROTOCOL

This contracted assessment of MTA for primary and secondary liver cancer addresses all of the PICO (Population, Intervention, Comparator and Outcomes) elements that were prespecified in the protocol that was ratified by PASC.

PROPOSED MEDICAL SERVICE

MTA uses electromagnetic waves at high frequency (900–2450 MHz) directed through thin antennae positioned in the centre of the tumour. The microwave radiation heats the water molecules in the tissue, causing cell death through coagulative necrosis. MTA can be conducted percutaneously, laparoscopically or intraoperatively. Imaging guidance using ultrasound or computed tomography scanning is required. According to the applicant, MTA is currently conducted as an inpatient procedure in public and private hospitals in Australia, and is usually performed by interventional radiologists or surgeons. It is usually provided in tertiary hospitals; however, MBS listing may lead to an extension of services in the private sector. The comparator, radiofrequency ablation (RFA), is currently funded for hepatocellular carcinoma (HCC).

PROPOSAL FOR PUBLIC FUNDING

The proposed item descriptors as provided in the PASC-approved final protocol for Populations 1 and 2, and using percutaneous, laparoscopic or open approach, are listed in Table 1. The protocol did not provide an item description for Population 3.

Table 1   Proposed MBS item descriptors

Category 3—THERAPEUTIC PROCEDURES
MBS [item number]   NON-RESECTABLE PRIMARY LIVER LESIONS, destruction of, by percutaneous microwave tissue ablation (MTA), including any associated imaging services, not being a service associated with a service to which item 30419, 50950 or 50952 (or other MTA items) applies   Fee: $TBA   [Relevant explanatory notes if required]
MBS [item number]   NON-RESECTABLE PRIMARY LIVER LESIONS, destruction of, by open or laparoscopic microwave tissue ablation (MTA), including any associated imaging services, where a multidisciplinary team has assessed that percutaneous microwave ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: —percutaneous access cannot be achieved;   —vital organs/tissues are at risk of damage from the percutaneous MTA procedure; or   —resection of one part of the liver is possible, but there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for microwave ablation, including any associated imaging services,   not being a service associated with a service to which item 30419, 50950 or 50952 (or other MTA items) applies   Fee: $TBA   [Relevant explanatory notes if required]
Category 3—THERAPEUTIC PROCEDURES
MBS [item number]   NON-RESECTABLE METASTATIC LIVER LESIONS, destruction of, by percutaneous microwave tissue ablation (MTA), including any associated imaging services,   not being a service associated with a service to which item 30419, 50950 or 50952 (or other MTA items) applies   Fee: $TBA   [Relevant explanatory notes if required]
MBS [item number]   NON-RESECTABLE METASTATIC LIVER LESIONS, destruction of, by open or laparoscopic microwave tissue ablation (MTA), including any associated imaging services, where a multidisciplinary team has assessed that percutaneous microwave ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: —percutaneous access cannot be achieved;   —vital organs/tissues are at risk of damage from the percutaneous MTA procedure; or   —resection of one part of the liver is possible, but there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for microwave ablation, including any associated imaging services,   not being a service associated with a service to which item 30419, 50950 or 50952 (or other MTA items) applies   Fee: $TBA   [Relevant explanatory notes if required]

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; TBA = to be arranged

POPULATION

There are three populations proposed for the use of MTA. In all of these groups, resection is not a therapeutic option; that is, all patients have unresectable tumours or lesions, regardless of their source. Population 1 comprises patients with primary liver lesions, of which there are four main

types: HCC, cholangiocarcinoma (CCA, cancer of the bile duct), angiosarcoma and hepatoblastoma. In Population 1, the intent of MTA is curative.

Population 2 comprises patients with secondary liver cancers, that is, metastases from primary cancers in other sites, most commonly colorectal cancer. In Population 2, the intent of MTA is curative.

Population 3 comprises patients with unresectable neuroendocrine liver metastases, with or without extrahepatic spread, who are refractory to somatostatin analogue therapy, in whom MTA is used for palliative treatment of secretory syndromes.

COMPARATOR DETAILS

For Population 1, RFA is the sole comparator. RFA is similar to MTA in that it uses a current, at a lower frequency than MTA (375–480 kHz), delivered down an electrode to heat and destroy tissue. The resources required for the delivery of RFA are similar to those of MTA, including the need for imaging to guide the procedure and equivalently qualified practitioners to deliver the treatment. RFA for patients with unresectable HCC is currently listed on the MBS (item 50950 for percutaneous approach and item 50952 for open or laparoscopic approach).

For Population 2, the comparator is RFA with or without adjuvant chemotherapy, or chemotherapy. RFA is not listed on the MBS for this population.

For Population 3, there are multiple comparators: RFA with or without adjuvant chemotherapy, chemotherapy, chemoembolisation, radioembolisation, radiolabelled somatostatin analogue therapy and, rarely, resection. The proposed population in the PASC-approved protocol described this population as 'unresectable' and 'refractory to somatostatin analogue therapy'; thus, resection and somatostatin analogue therapy were unlikely to be found as comparators. RFA is not listed on the MBS for this population.

CLINICAL MANAGEMENT ALGORITHM(S)

According to the clinical management algorithm provided in the protocol, MTA would be a direct substitution for RFA in indicated patients, with no other expected management changes. It is not expected that the MBS listing of MTA would result in any change in the number of patients indicated for ablation.

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Aside from different equipment, the delivery and organisation of care for patients undergoing MTA would be the same as for patients undergoing RFA.

CLINICAL CLAIM

The clinical claim is that MTA is a safer and more effective therapy than its comparator, RFA, for treating primary and secondary liver cancer. This claim is based on MTA's ability to provide more predictable ablation volume shapes and sizes, reducing the potential for compromise of healthy hepatic and extrahepatic tissue; larger ablation volumes in faster times; and reduced risk of burning and the heat sink effect.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published literature was undertaken. The databases searched included PubMed, EMBASE, Cochrane Library, Web of Science and Current Contents. The searches were undertaken on 10 May 2016. The search was restricted by publication year (1990 onwards); however, there were no other restrictions on the search, which was kept broad so as to capture the three populations considered in the assessment. The search strategy can be viewed in Appendix C. Two authors performed the study selection, based on the PICO criteria, and a third author conducted a duplicate-cull of the most relevant 10 per cent of the references, as determined by the algorithms in Rayyan software to ensure that no studies had been missed; none were identified. In addition, relevant systematic reviews (SRs) were pearled to ensure that no studies were missed. Two authors applied relevant critical appraisal tools based on study types.

CHARACTERISTICS OF THE EVIDENCE BASE

The studies identified and included to assess the safety and effectiveness of MTA to treat liver tumours are summarised in Table 2. Four SRs were identified, containing 19 individual studies, providing very recent Level I evidence for this assessment.

Table 2   Summary of studies included in evidence base

Population	Studies (*K*)	NHMRC level of evidence	Comments
1	*K* = 4 SRs incl 19 discrete studies	Level 1 (as SRs include RCTs, but most evidence level III)	Quality of SRs high, but many included studies had historical controls
	K = 6 non-randomised comparative cohort studies	Level III-2 and III-3	Cohort studies of moderate quality; many with historical controls
	K = 1 case series	Level IV	
2	*K* = 1 non-randomised comparative cohort study	Level III-2	Moderate quality; concurrent controls
	K = 12 case series	Level IV	Poor to moderate quality
3	*K* = 0		NA

NA = not applicable; NHMRC = National Health and Medical Research Council; RCT = randomised controlled trial; SR = systematic review

RESULTS

Safety

The evidence from two SRs in percutaneous ablation was consistent in finding a higher number of overall major adverse events in patients undergoing MTA than RFA; however, the differences were

not statistically significant, and as the rates were low, the differences are unlikely to be of clinical importance.

Two comparative non-randomised studies that examined patients undergoing surgical ablation found higher rates of adverse events than in percutaneous ablation, in both the MTA and RFA groups, and inconsistent findings between studies. These studies were relatively small, and it is not clear whether the adverse events were defined in a similar way in each study. It is difficult to draw conclusions about the safety of MTA versus RFA in surgical ablation from these data.

No comparative safety data specific to Population 2 or 3 was identified, other than a mention of no procedure-related mortality in either group in the one comparative study. No conclusions can be drawn about the safety of MTA in these populations. As it is likely that the patients in these groups have more complex disease and are more unwell than those in Population 1, it is difficult to judge whether the safety profile for MTA in this group would be similar to that for Population 1.

Effectiveness

Overall, the evidence for Population 1 was consistent in reporting few clinically or statistically significant differences between MTA and RFA in this patient group. The findings are summarised in Table 3.

For percutaneous ablation, the SRs were very consistent in their results across the primary outcome measures of local tumour recurrence, complete ablation, overall survival and recurrence-free survival, finding few statistically significant differences between MTA and RFA. The additional comparative studies also provided similar evidence for most outcomes. In studies including patients undergoing surgical ablation, data reporting was limited, but in two studies that reported either rates of recurrence or the relative risk of recurrence, there was no difference between the treatments.

There was some evidence that MTA was superior to RFA in patients with more severe classification of cancer for tumour recurrence; however, as most studies had historical controls, the result could also be due to other changes in cancer treatment over that time, resulting in better outcomes for patients with more severe disease.

Limited data on secondary outcomes were identified; in particular, there was a paucity of data supporting claims that MTA required less ablation time and fewer sessions.

For Population 2, one comparative study found a difference likely to be clinically meaningful, but not statistically significant, favouring MTA for local tumour recurrence. It also found better overall survival in years 2 and 5 for patients who had MTA, although these results were not statistically significant, and the small number of patients in this study makes the results difficult to interpret.

There is no evidence in Population 3 to enable any conclusions to be drawn about the effectiveness of MTA in this patient group.

Table 3 **Balance of clinical benefits and harms of MTA, relative to RFA, as measured by the <u>critical</u> patient-relevant outcomes in the key studies for Population 1**

Outcomes Follow-up	Studies (*K*) Participants (*P*)	Quality of evidence (GRADE)[a]	Range of results :OR/HR and 95% CI, *P* value	Comments
Local tumour recurrence—percutaneous	*K* = 3 SR *K* = 2 RHCC	⊕⊕⊙⊙	ORs between 1.01 (0.67, 1.50) and 1.17 (0.61, 2.24) ORs between 0.91 and 1.13 (95% CI not reported) HR 2.17 (1.04, 4.50) *P* = 0.04	No difference between groups
Local tumour recurrence—surgical	*K* = 2 RHCC *K* = 1 RCCC	⊕⊙⊙⊙	MTA 0–23% vs RFA 9.1–25.5% with events	No difference between groups
Overall survival 1 year—percutaneous	*K* = 2 SR	⊕⊕⊙⊙	ORs between 1.11 (0.36, 3.47) and 1.36 (0.73, 2.54)	No difference between groups
Overall survival 3 years—percutaneous	*K* = 3 SR	⊕⊕⊙⊙	ORs between 0.58 (0.32–1.07) and 0.95 (0.58, 1.57)	No difference between groups

Recurrence-free survival—percutaneous:
    1 year
    3 years
    5 years
	K = 1 SR
	
	N = 668
	N = 596
	N = 353
		⊕⊕⊙⊙	
			
			OR 0.79 (0.56, 1.13), *P* = 0.20
			OR 1.03 (0.73, 1.45), *P* = 0.99
			OR 0.60 (0.39, 0.94), *P* = 0.03
				No difference between groups except at 5 y

Complete ablation—percutaneous	*K* = 3 SR	⊕⊕⊙⊙	ORs between 0.98 (0.85, 1.14) and 1.12 (0.67, 6.07)	No difference between groups
Major adverse events—percutaneous	*K* = 2 SR *K* = 1 RCCC	⊕⊕⊙⊙	OR 0.63 (0.29,1.38)—note MTA was the comparator OR 1.63 (0.88,3.03), *P* = 0.12 OR 0.88 (0.43, 1.79), *P* = 0.73[b]	No difference between groups; low event rates
Major adverse events—surgical	*K* = 2 RHCC	⊕⊙⊙⊙	ORs between 0.35 (0.10, 1.20), *P* = 0.09, and 1.92 (0.47, 7.77), *P* = 0.36[b]	No difference between groups; small studies
Procedure-related deaths—percutaneous	*K* = 1 RCCC	⊕⊕⊙⊙	OR 1.16 (0.10, 12.87), *P* = 0.90[b]	No difference between groups; very low rates

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HR = hazard ratio; MTA = microwave tissue ablation; RHCC = retrospective historical control cohort; RCCC = retrospective concurrent control cohort; OR = odds ratio; RFA = radiofrequency ablation; SR = systematic review

[a] GRADE Working Group grades of evidence (Guyatt et al 2013):

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: the true effect may be substantially different

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different
[b] ORs and CIs calculated from published figures

On the basis of the benefits and harms reported in the evidence base (summarised above), **it is suggested that, relative to RFA, MTA has non-inferior safety and non-inferior effectiveness in Population 1.** On the basis of limited evidence, **it is suggested that, relative to RFA, MTA has non-**

inferior safety and non-inferior effectiveness in Population 2. There is insufficient evidence to determine the safety and effectiveness of MTA, relative to RFA, in Population 3.

TRANSLATION ISSUES

The selection of the most applicable evidence to the Australian setting is discussed in the economic analysis section on inputs (Section D.4); no additional evidence translations were required.

ECONOMIC EVALUATION

The comparative evidence did not identify a significant difference in outcomes in Population 1 or 2, and justified the assumption that health outcomes would be equivalent across each arm of the economic evaluation. Therefore, the economic evaluation aimed to calculate the cost of providing MTA compared with RFA in Population 1, and MTA with or without chemotherapy compared with RFA with or without chemotherapy in Population 2, and present this as a cost-minimisation approach. Table 4 describes the key constructs of the economic evaluation that is provided in the assessment report.

Table 4   Summary of the economic evaluation

Perspective	Australian healthcare
Comparator	Radiofrequency ablation
Type of economic evaluation	Cost-minimisation
Sources of evidence	Systematic review, section B.5a–6a, B.5.b–6.b
Outcomes	Cost per patient
Methods used to generate results	Cost comparisons
Software packages used	Microsoft Excel 2013

Key assumptions in the economic analysis are that the preoperative and postoperative follow-up costs, adverse event rates, and comorbidities and their associated impact on perioperative and postoperative patient management are all similar across MTA and RFA, and are therefore not included in the analysis.

On the basis of the non-inferiority conclusion, it was advised that funding for MTA should be consistent with RFA[1]. The current funding of RFA is determined by the scheduled fees for MBS items 50950 and 50952, both of which are currently set at $817.10 per service.

Table 5 shows the overall costs and incremental cost per patient as calculated for the intervention and comparator in the analysis, with the base-case assumptions.

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[1] Commonwealth feedback to the draft report for MSAC Application 1402; email received on 4 August 2016.

Table 5   Costs associated with MTA and RFA

Item description	MTA	RFA
Ablation procedure	$817	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Chemotherapy	$805	$805
Other hospital costs	$6,236	$6,236
Population 1[1]	**$7,235**	**$7,235**
Population 2	**$8,039**	**$8,039**

[1] Cost associated with procedures for population 1 excludes cost of chemotherapy

MTA = microwave tissue ablation; RFA = radiofrequency ablation

Univariate sensitivity analyses are presented in Table 6, and include assessment of the cost impact of varying costs associated with procedures: MBS fees charged (stratified on the basis of number of lesions), hospital costs, anaesthesia cost and number of ablation sessions required (for further details, see sections D.6.a and D.6.b). An additional sensitivity analysis was also performed assuming a 10 per cent relative reduction in chemotherapy usage with MTA for Population 2. As seen in Table 6, the cost variations for the included parameters can result in either net costs or net savings to the MBS.

Table 6   One-way sensitivity analyses of key parameters

Sensitivity analyses	Incremental cost per patient (Population 1)	Incremental cost per patient (Population 2)
Base case	**$0**	**$0**
Weighted MBS fee of MTA[1]	$145	$290
Reducing hospital costs of MTA by 10%[2]	−$624	−$624
Reducing hospital costs of MTA by 20%[2]	−$1,247	−$1,247
Reducing 1 basic unit of anaesthesia for MTA[2]	−$20	−$20
Reducing 2 basic units of anaesthesia for MTA[2]	−$40	−$40
Number of MTA sessions required per patient: 2.4[3]	$10,129	$11,255
Number of RFA sessions required per patient: 1.2[3]	−$1,447	−$1,608
Number of RFA sessions required per patient: 2	NR	−$8,039
Relative reduction of 10% in chemotherapy usage with MTA[4]	NR	−$152

[1] Weighted MBS fee of $962 for population 1 (based on stratified fee of $817 for treatment of ≤3 lesions and $1,300 for >3 lesions) and of $1,107 for population 2 (based on stratified fee of $817 for treatment of ≤5 lesions and $1,300 for >5 lesions). For further details see section D.4.

[2] As per applicant and some clinicians' suggestions, MTA would result in cost savings associated with operating/procedure rooms, as it allows faster ablation times than RFA. Sensitivity analyses are performed assuming arbitrary decreases of 10% and 20% in hospital costs associated with MTA and reducing basic anaesthesia units used during the procedure.

[3] The number of sessions required per patient for RFA (1.2) estimated from MBS data received from the Department of Health and for MTA (2.4) sourced from (Shibata et al 2002b). See section D.4.4 for further details.

[4] One consultant suggested that the use of MTA may reduce the chemotherapy usage by 10% compared with RFA.

Shaded cells show the cost savings (negative value for incremental cost) by MTA.

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; NR = not relevant; RFA = radiofrequency ablation

Estimated Extent of Use and Financial Implications

An epidemiological approach has been used to estimate the financial implications of the introduction of MTA. The financial implications to the MBS resulting from the proposed listing of MTA (assuming similar MBS funding for MTA as for RFA) are summarised in Table 7.

Table 7   Total costs to the MBS associated with MTA

-	2015–16	2016–17	2017–18	2018–19	2019–20
Population 1					
Number of services	130	145	160	176	194
Subtotal cost	$83,070	$92,791	$102,437	$112,952	$124,030
Population 2					
Number of services	45	48	52	57	61
Subtotal cost	$27,305	$29,683	$32,123	$34,625	$37,187
Total services	**175**	**193**	**212**	**233**	**255**
Total cost	**$110,375**	**$122,474**	**$134,560**	**$147,577**	**$161,217**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation;

Consumer Impact Summary

Following public consultation there were six responses from individuals, including one consumer, four treating specialists and one specialist/researcher. Responses were all in favour of including primary and secondary tumours in the proposed MBS items. It was evident from feedback that MTA is already used on a regular basis for the treatment of liver tumours in Australia and other industrialised countries.

ACRONYMS AND ABBREVIATIONS

Acronym/abbreviation	Meaning
ACIM	Australian Cancer Incidence and Mortality
AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews (quality assessment tool)
AR-DRG	Australian Refined Diagnostic Related Group
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
AUD	Australian dollars
CCA	cholangiocarcinoma
CI	confidence interval
CRC	colorectal cancer
CRLM	colorectal liver metastases
CS	case series
CT	computed tomography
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	hepatocellular carcinoma
MBS	Medicare Benefits Schedule
MRI	magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MTA	microwave tissue ablation
NHCDC	National Hospital Cost Data Collection
NHMRC	National Health and Medical Research Council
NHS CRD	UK National Health Service Centre for Reviews and Dissemination
OR	odds ratio
OS	overall survival
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PICO	Population, Intervention, Comparator and Outcomes
RCT	randomised controlled trial
RFA	radiofrequency ablation
RHCC	retrospective historical control cohort
RR	relative risk
SD	standard deviation
TACE	transcatheter arterial chemoembolisation
US	ultrasound

Section A Context

This contracted assessment of microwave tissue ablation (MTA) for the treatment of primary and secondary liver tumours is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

Adelaide Health Technology Assessment has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of MTA for the treatment of primary and secondary liver tumours. This assessment has been undertaken in order to inform MSAC's decision making regarding whether the proposed medical service should be publicly funded.

Appendix A provides a list of the people involved in the development of this assessment report, including the experts who provided clinical expertise.

The proposed use of MTA for the treatment of primary and secondary liver tumours in Australian clinical practice was outlined in a protocol that was presented to, and accepted by, the Protocol Advisory Sub-Committee (PASC) of the MSAC. The consultation protocol was released for public comment in October 2015.

A.1. Items in the Agreed Protocol

This contracted assessment of MTA for primary and secondary liver tumours addresses most of the PICO (Population, Intervention, Comparator, Outcomes) elements that were prespecified in the protocol that was ratified by PASC.

To comply with the PICO, initially only studies including patients with *unresectable* liver tumours were to be included for populations 1 and 2 (patients with primary or secondary unresectable liver tumours). However, between 70 and 90 per cent of liver tumours are reported to be unresectable, owing to comorbidity and poor liver function (Boutros et al 2010; Kim et al 2016). Therefore, this criterion was not enforced for articles that were otherwise eligible for inclusion, as it was assumed that the majority of the included populations had at least 70 per cent unresectable tumours.

A.2. Proposed Medical Service

MTA uses electromagnetic radiation within the ultra-high-frequency band of the radio spectrum to effect destruction of tumour tissue at a cellular level. MTA is generally performed using devices

producing frequencies between 915 MHz and 2.45 GHz (Brace 2010). In Australia, there are four companies with Therapeutic Goods Administration–registered MTA devices available for use (Table 8), all of which use frequencies within this range (MSAC 2016). Thermal radiation created at these frequencies is transmitted via a needle-like antenna inserted into the tumour, performed percutaneously or by accessing the tumour through laparoscopic or open surgery. Tissue death itself is achieved through radiated microwave-generated heat causing cellular coagulative necrosis.

In Australia, MTA for liver tumours can be performed within a private or public hospital setting, on patients under general anaesthesia who will usually require an overnight stay, or in a day surgery. The procedure may be carried out either by an appropriately qualified surgeon or an interventional radiologist, and can be performed percutaneously or with laparoscopic or open surgical techniques. MTA is normally performed with the assistance of ultrasound for the location of tumours and monitoring of heat transfer (Boutros et al 2010; Brace 2010). Expert advice is that MTA is usually provided in tertiary hospitals and is highly unlikely to be performed in regional centres; however, PASC noted the applicant's advice that if Medicare funding were approved, there may be some extension of services in the private sector.

There are thought to be several advantages of microwave over other thermal ablation techniques. Higher temperatures can be reached in a shorter time period, thereby enabling shorter treatment times for patients. MTA can achieve a higher temperature than radiofrequency ablation (RFA) and thus treat larger areas. Microwaves can be transmitted through tissue with varying water composition and are less susceptible to the heat sink effect, which can occur in well vascularised tissues. There may be drawbacks with MTA related to rapid heating and high temperatures, which can create a safety concern. Cable and antenna cooling can help prevent burns and destruction of healthy tissue (Brace 2010).

MTA is also known as microwave ablation, microwave thermal ablation, microwave coagulation therapy, microwave ablation therapy, and microwave tissue coagulation. This report consistently uses MTA, even when the original studies use a different name for the technique.

MARKETING STATUS OF DEVICE / TECHNOLOGY

Several MTA systems are registered on the Australian Register of Therapeutic Goods for coagulation of soft tissue or lesions (Table 8). Other registered devices are intended for treatment of diseases other than liver lesions; e.g. benign prostate hyperplasia.

Table 8   Microwave tissue ablation systems listed on the Australian Register of Therapeutic Goods (ARTG)

ARTG ID	Product no.	Product description	Product category	Sponsor
157722	40783	Acculis hyperthermia system, microwave (2450 MHz, 140 W)	Medical Device IIb	N Stenning and Co Pty Ltd
174514	40792	Hyperthermia applicator, microwave, intracorporeal	Medical Device IIb	N Stenning and Co Pty Ltd
174513	40797	Probe, hyperthermia, temperature monitor	Medical Device IIa	N Stenning and Co Pty Ltd
200325	40783	Avecure Microwave Ablation / Coagulation System—Hyperthermia system, microwave (902–928 MHz, 32 W)	Medical Device IIb	Aurora BioScience Pty Ltd
226598	40783	Emprint™ Ablation System with Thermosphere™ Technology, microwave hyperthermia system (1400–1500 MHz, 100 W)	Medical Device IIb	Covidien Pty Ltd
152044	40783	Hyperthermia system, microwave	Medical Device IIb	Covidien Pty Ltd
178699	40783	Evident™ Hyperthermia system, microwave	Medical Device IIb	Covidien Pty Ltd
178369	40792	Hyperthermia applicator, microwave, intracorporeal	Medical Device IIb	Covidien Pty Ltd
212509	40783	Amica hyperthermia system, microwave (2450 MHz, 20–140 W)	Medical Device IIb	Culpan Medical Pty Ltd
212510	40792	Hyperthermia applicator, microwave, intracorporeal	Medical Device IIb	Culpan Medical Pty Ltd

Source: Therapeutic Goods Administration, accessed 26 July 2016

OTHER INDICATIONS

Microwave therapy is subsidised by the MBS for ablation of the endometrium to treat chronic refractory menorrhagia (item 35616) and for thermotherapy of the prostate (items 37230 and 37233).

An application to MSAC for listing of MTA of the lung (item 1403) is currently being assessed.

CURRENT FUNDING ARRANGEMENTS

Currently there is no public funding for MTA for the treatment of liver cancer. The primary comparator for MTA, RFA, is currently funded for patients with unresectable hepatocellular carcinoma (HCC) under two MBS items (50950 and 50952) which allow for percutaneous, laparoscopic or open surgical application. Hospital data indicate that patients receiving RFA as an outpatient (approximately 40 per cent) are bulk-billed and have therefore not been required to make co-payments, and gap costs for patients receiving in-hospital treatment are absorbed by the hospital system or covered by private insurance. It is likely that MTA would be funded in a similar way should it be listed for subsidy (refer to Table 39 for 2010–2015 hospital data).

A.3.   PROPOSAL FOR PUBLIC FUNDING

Table 9 contains the proposed MBS item descriptors from the protocol ratified by PASC for
unresectable liver lesions (Population 1), and unresectable metastatic liver tumours (Population 2)
are outlined in Table 10. They cover patients with unresectable liver lesions or metastatic tumours
who undergo the procedure percutaneously or by laparoscopic or open surgery. Note that no item
descriptor for Population 3—patients with unresectable neuroendocrine liver lesions with
extrahepatic spread, refractory to somatostatin analogues requiring palliative treatment for
secretory syndromes—was provided.

**Table 9   Proposed MBS items for percutaneous, laparoscopic or open surgical microwave tissue ablation for
unresectable primary liver lesions**

Category 3—THERAPEUTIC PROCEDURES
MBS [item number]
NON-RESECTABLE PRIMARY LIVER LESIONS, destruction of, by percutaneous microwave tissue ablation (MTA), including any associated imaging services, not being a service associated with a service to which items 30419, 50950, 50952 or (other MTA items) applies
Fee: $TB
[Relevant explanatory notes if required]
MBS [item number]
NON-RESECTABLE PRIMARY LIVER LESIONS, destruction of, by open or laparoscopic microwave tissue ablation (MTA), including any associated imaging services, where a multidisciplinary team has assessed that percutaneous microwave ablation cannot be performed or is not practical because of one or more of the following clinical circumstances:
—percutaneous access cannot be achieved
—vital organs/tissues are at risk of damage from the percutaneous MTA procedure
—resection of one part of the liver is possible, however, there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for microwave ablation, including any associated imaging services
not being a service associated with a service to which items 30419, 50950, 50952 or (other MTA items) applies
Fee: $TBA
[Relevant explanatory notes if required]

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; TBA = to be arranged

Table 10   Proposed MBS item for percutaneous, laparoscopic or open surgical microwave tissue ablation for unresectable metastatic liver tumours

Category 3—THERAPEUTIC PROCEDURES
MBS [item number]
NON-RESECTABLE METASTATIC LIVER LESIONS, destruction of, by percutaneous microwave tissue ablation (MTA), including any associated imaging services, not being a service associated with a service to which items 30419, 50950, 50952 or (other MTA items) applies
Fee: $TBA
[Relevant explanatory notes if required]
MBS [item number]
NON-RESECTABLE METASTATIC LIVER LESIONS, destruction of, by open or laparoscopic microwave tissue ablation (MTA), including any associated imaging services, where a multidisciplinary team has assessed that percutaneous microwave ablation cannot be performed or is not practical because of one or more of the following clinical circumstances: —percutaneous access cannot be achieved   —vital organs/tissues are at risk of damage from the percutaneous MTA procedure   —resection of one part of the liver is possible, however, there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for microwave ablation, including any associated imaging services   not being a service associated with a service to which items 30419, 50950, 50952 or (other MTA items) applies
Fee: $TBA
[Relevant explanatory notes if required]

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; TBA = to be arranged

A.4.   PROPOSED POPULATION

The protocol identifies three populations that are treated for unresectable primary or secondary liver tumours, each of which is treated through a different clinical pathway and has different comparators in clinical practice:

- Population 1: Patients with unresectable primary liver lesions in whom MTA is used with curative intent

- Population 2: Patients with unresectable secondary liver lesions, without extrahepatic spread, in whom MTA is used with curative intent

- Population 3: Patients with unresectable neuroendocrine liver metastases, with or without extrahepatic spread, who are refractory to somatostatin analogue therapy, in whom MTA is used for palliative treatment of secretory syndromes

There is some variability regarding the definition of 'unresectable' tumours and the contraindications to resectability. In the agreed protocol, the applicant suggests criteria clarifying the term 'unresectable' liver cancer. A patient may be considered to have unresectable liver cancer when surgical resection is not possible owing to the presence of liver malignancy in unresectable locations, the number and anatomical distribution of tumour lesions, and/or the presence of extrahepatic disease (metastatic neuroendocrine tumours only) or poor liver function (Hemming & Gallinger 2001; Orloff 1981). The literature indicates, however, that between 70 and 90 per cent of

liver tumours are reported to be unresectable owing to comorbidity and poor liver function (Boutros et al 2010; Kim et al 2016). In the light of this data, the criteria for unresectability were not strictly applied; however, studies in which the majority of patients also received resection were excluded.

PASC asked that the delivery of ablation via the percutaneous route be considered separately to the open or laparoscopic approach; this is reflected in the research questions listed in Section A.9.

PRIMARY LIVER CANCER

The incidence of primary liver cancer is on the rise in Australia. Between 1982 and 2014, the age-standardised incidence rate for liver cancer increased from 1.8 to 6.4 per 100,000 (AIHW 2014). The age-standardised mortality rate for the same period increased from 2.3 to 6.0 per 100,000. Further Australian data indicate that the incidence of liver cancer is 2.8 times as high in indigenous as in non-indigenous Australians, and 2.8 times as high in men as in women. In 2011, the incidence of liver cancer was 1041 per 100,000 in men compared with 406 per 100,000 in women, while the mortality rates (2012) were 976 per 100,000 in men compared with 514 per 100,000 in women (AIHW 2014).

HCC is by far the most common type of primary liver cancer, accounting for 80 per cent of cases, and is caused mainly by infection by hepatitis A, B or C virus. Aflatoxin B_1 and alcohol consumption can also lead to HCC (ASCO 2014; Forner, Llovet & Bruix 2012). Cholangiocarcinoma (CCA, cancer of the bile duct) is the second most frequent type of liver cancer, making up 10 to 20 per cent of cases. Angiosarcoma and hepatoblastoma are more rare forms (ASCO 2014).

SECONDARY LIVER CANCER

The majority of liver tumours are secondary in origin, arising as metastases from a number of different cancers. The most common of these is colorectal cancer (CRC), which causes liver metastases in about 50 per cent of patients over the course of their disease (Prenen & Van Cutsem 2012). Metastases originating in neuroendocrine tumours of secretory organs such as the lungs and gastrointestinal tract make up as much as 10 per cent of all liver metastases (Lee, SY et al 2012). Other sources include non-neuroendocrine cancer types such as breast carcinoma, renal carcinoma, gynaecological tumours, gastrointestinal stromal tumours, oesophageal carcinoma, gastric carcinoma, exocrine pancreatic carcinoma, lung cancer, melanoma and testicular tumours.

Data for secondary liver disease in Australia cannot be separated from data for primary liver cancer. However, a US literature review reported that lung, colon, pancreas, breast and stomach carcinomas accounted for 24.8, 15.7, 10.9, 10.1 and 6.1 per cent of metastases in one autopsy series (Ishak, Goodman & Stocker 2001), with lesser contributions from ovarian, endometrial, prostate and urothelial carcinomas (Centeno 2006).

A.5. COMPARATOR DETAILS

For the treatment of liver lesions, the gold standard is considered to be surgical resection (Bhardwaj et al 2010). For patients who have unresectable primary tumours (Population 1), there is currently available the Medicare-subsidised treatment of RFA (percutaneous or surgical), which is the main comparator for this assessment. For patients with unresectable secondary tumours (Population 2), there is no Medicare-subsidised treatment; however, RFA (percutaneous or surgical) is the current treatment. RFA is offered to Population 2 with or without chemotherapy, and chemotherapy is a second comparator for this group. For Population 3, MTA is considered a palliative rather than curative treatment, and RFA (percutaneous or surgical) is currently one treatment offered. Additional comparators for this population are chemotherapy, chemoembolisation, radioembolisation, radiolabelled somatostatin analogue therapy and resection, although there are no Medicare-funded treatments at this time. The MBS item descriptors for the relevant comparator are summarised in Table 11.

Table 11   MBS items for radiofrequency ablation

Category 3—THERAPEUTIC PROCEDURES
MBS 50950   NON-RESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by percutaneous radiofrequency ablation, including any associated imaging services, not being a service associated with a service to which item 30419 or 50952 applies   Fee: $817.10   [Relevant explanatory notes]
MBS 50952   NON RESECTABLE HEPATOCELLULAR CARCINOMA, destruction of, by open or laparoscopic radiofrequency ablation (RFA), where a multidisciplinary team has assessed that percutaneous RFA cannot be performed or is not practical because of one or more of the following clinical circumstances: —percutaneous access cannot be achieved;   —vital organs/tissues are at risk of damage from the percutaneous RFA procedure; or   —resection of one part of the liver is possible, however, there is at least one primary liver tumour in a non-resectable region of the liver which is suitable for RFA, including any associated imaging services, not being a service associated with a service to which item 30419 or 50950 applies   Fee: $817.10   [Relevant explanatory notes if required]

MBS = Medicare Benefits Schedule; RFA = radiofrequency ablation

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

The clinical management algorithms agreed to by PASC are shown in Figure 1 to Figure 6 in Appendix B. It is expected that MTA would be a direct substitution for RFA in the clinical algorithm, with no other changes to patient selection or management expected.

A.7. KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

MTA is expected to fully replace the use of RFA in the populations proposed in the PICO. It is expected that MTA would be offered within the same delivery setting as RFA.

A.8. CLINICAL CLAIM

The applicant claims that MTA is superior to RFA in both safety and effectiveness.

More specifically, it claims that MTA produces more predictable ablation volume shapes and sizes than RFA, reducing the potential for compromise of healthy liver tissue and extrahepatic tissue injury (Bhardwaj et al 2010). In addition, MTA is claimed to have a steeper temperature gradient, with tissue temperatures reaching >200 °C, and faster conduction than RFA (Simo, K et al 2012). This has the potential to enable larger ablation volumes in a shorter treatment time.

It is further suggested there is a lower risk of complications with MTA than with RFA, as MTA does not involve electricity or grounding pads, thus reducing the risk of burns. MTA technology is additionally claimed to be less susceptible to the heat sink effect owing to its ability to reach high ablation temperatures in fast times (Bhardwaj et al 2010).

A.9. SUMMARY OF THE PICO

The guiding framework of PICO (Population, Intervention, Comparator and Outcomes) criteria is recommended by MSAC for each assessment. The PICO criteria describe current clinical practice and reflect the likely future practice with the proposed medical service.

The PICO criteria that were prespecified to guide the systematic literature review are presented in Box 1 for Population 1, Box 2 for Population 2 and Box 3 for Population 3. Research questions follow the individual PICO boxes.

Box 1   Criteria for identifying and selecting studies to determine the safety and effectiveness of MTA in patients with unresectable primary liver tumours (Population 1)

Selection criteria	Description
Population	Patients with unresectable primary liver lesions
Intervention	Microwave tissue ablation (MTA) of the liver (percutaneous OR laparoscopic/open)
Comparator	Radiofrequency ablation (RFA) of the liver (percutaneous OR laparoscopic/open)
Outcomes	Primary effectiveness: tumour recurrence, percentage of lesions with complete ablation, overall survival (short term and long term), recurrence-free survival (short term and long term), need for repeat ablation, accuracy of ablation margins.
	Secondary effectiveness: procedure time, length of hospital stay, recovery time, patient discomfort,

Selection criteria	Description
	quality of life
	Safety: rate of adverse events (including bleeding, bile duct injury or stenosis, wound dehiscence, pain, postoperative ascites, skin burns, liver abscess, hepatic infarction, colonic perforation, deterioration in liver function, damage to adjacent organs, pneumothorax, pleural effusion, fever), procedure-related mortality

Research questions for Population 1
In patients with unresectable primary liver lesions, what are the safety, effectiveness and cost-effectiveness of percutaneous MTA compared with RFA?
In patients with unresectable primary liver lesions, what are the safety, effectiveness and cost-effectiveness of open or laparoscopic MTA compared with RFA?

Box 2   Criteria for identifying and selecting studies to determine the safety and effectiveness of MTA in patients with unresectable secondary liver tumours (Population 2)

Selection criteria	Description
Population	Patients with unresectable metastatic liver disease without extrahepatic spread
Intervention	Microwave tissue ablation (MTA) of the liver (percutaneous OR laparoscopic/open) with curative intent, with or without adjuvant chemotherapy
Comparator	Radiofrequency ablation (RFA) of the liver (percutaneous OR laparoscopic/open) (with or without chemotherapy)
	Chemotherapy
Outcomes	Primary effectiveness: tumour recurrence, percentage of lesions with complete ablation, overall survival (short term and long term), recurrence-free survival (short term and long term), need for repeat ablation, accuracy of ablation margins
	Secondary effectiveness: procedure time, length of hospital stay, recovery time, patient discomfort, quality of life
	Safety: rate of adverse events (including bleeding, bile duct injury or stenosis, wound dehiscence, pain, postoperative ascites, skin burns, liver abscess, hepatic infarction, colonic perforation, deterioration in liver function, damage to adjacent organs, pneumothorax, pleural effusion, fever), procedure related mortality

Research questions for Population 2
In patients with unresectable liver metastases without extrahepatic spread, what are the safety, effectiveness and cost-effectiveness of percutaneous MTA with curative intent (with or without chemotherapy) of liver tumours compared with RFA, chemotherapy or both?
In patients with unresectable liver metastases without extrahepatic spread, what are the safety, effectiveness and cost-effectiveness of open or laparoscopic MTA with curative intent (with or without chemotherapy) of liver tumours compared with RFA, chemotherapy or both?

Box 3 Criteria for identifying and selecting studies to determine the safety and effectiveness of MTA in patients with patients with unresectable neuroendocrine liver metastases (Population 3)

Selection criteria	Description
Population	Patients with unresectable neuroendocrine liver lesions, with extrahepatic spread, refractory to somatostatin analogues requiring palliative treatment for secretory syndromes
Intervention	Microwave tissue ablation (MTA) of the liver (percutaneous OR laparoscopic/open)
Comparator	Radiofrequency ablation (RFA) of the liver (percutaneous OR laparoscopic/open) Chemotherapy Chemoembolisation Radioembolisation Radiolabelled somatostatin analogue therapy Resection (rare)
Outcomes	Primary effectiveness: symptom reduction, quality of life, median survival Safety: rate of adverse events (including bleeding, bile duct injury or stenosis, wound dehiscence, pain, postoperative ascites, skin burns, liver abscess, hepatic infarction, colonic perforation, deterioration in liver function, damage to adjacent organs, pneumothorax, pleural effusion, fever)

Research questions for Population 3
In patients with unresectable neuroendocrine liver metastases (with or without extrahepatic spread) with secretory syndromes refractory to somatostatin analogues requiring palliative treatment, what are the safety, effectiveness and cost-effectiveness of percutaneous MTA of liver tumours compared with RFA, chemotherapy, chemoembolisation, radioembolisation, or radiolabelled somatostatin analogue therapy? In patients with unresectable neuroendocrine liver metastases (with or without extrahepatic spread) with secretory syndromes refractory to somatostatin analogues requiring palliative treatment, what are the safety, effectiveness and cost-effectiveness of open or laparoscopic MTA of liver tumours compared with RFA, chemotherapy, chemoembolisation, radioembolisation, or radiolabelled somatostatin analogue therapy?

A.10. CONSUMER IMPACT STATEMENT

Following public consultation, there were six responses: from one consumer, four treating specialists and one specialist researcher. Responses were all in favour of including primary and secondary tumours in the proposed MBS items. One respondent noted that in the case of metastatic liver nodules, treatment was valuable despite the presence of extrahepatic nodules, as preservation of a healthy liver had the potential to extend life. One specialist recommended the removal of the 'unresectable' restriction to the eligible population, as in his opinion in some cases patients resectable tumours can benefit from undergoing MTA rather than resection. It was evident from feedback that MTA is already used on a regular basis for the treatment of liver tumours in Australia and other industrialised countries.

In general the agreed advantages of MTA to the patients were:

- Lower negative impact on patient due to frequent performance of MTA as an outpatient procedure, requiring less sedation, often no anaesthetic and reduced recovery time.
- Lower costs to patients due to reduced hospital time and less need for full anaesthetic.
- Faster and more predictable procedure than RFA.
- Less burden on the hospital system as fewer beds are required owing to faster treatment and lower recovery time.
- No need for the leg pads required for RFA, and therefore less risk of burns.

One disadvantage was reported:

- If MTA is not performed correctly, there may be a higher rate of local recurrence.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The peer reviewed medical literature was searched on 10 May 2016 to identify relevant studies and systematic reviews published during the period January 1990 to the date of the search. Relevant Health Technology Assessment and specialty websites were also searched. The databases and sources searched are listed in Appendix C. The search was not restricted by comparator or outcome criteria, nor by language of original publication. Articles in languages other than English were included only if they were of a higher level of evidence than English language articles identified, according to the abstract. Search terms used to identify the population and intervention were kept deliberately broad so as to capture studies which included any of the three populations under investigation in this assessment. Search terms are described in Table 12. Pearling of relevant articles and reviews was performed to maximise access to studies that were likely to be eligible.

Table 12   Search terms used (PubMed platform)

Element of clinical question	Search terms
Population	(liver OR liver[MeSH] OR hepat*) AND (tumour OR tumor OR tumor[MeSH] OR lesion OR neoplasm OR neoplasm[MeSH] OR cancer OR carcino* OR onco*)
Intervention	microwave OR microwaves[MeSH] OR MTA OR MWA OR radiofrequency OR 'radio frequency' OR electrocoag* OR radio waves[MeSH] OR short-wave therapy[MeSH] OR 'radio waves' OR 'short-wave therapy'
Comparator (if applicable)	No limits
Outcomes (if applicable)	No limits
Limits	Published 1990 onwards
Language	No limits[a]

MeSH = Medical Subject Heading, based on a MEDLINE/PubMed platform; MTA = microwave tissue ablation; MWA = microwave ablation

[a] Non-English articles were included if the English language abstract indicated that the study was of a higher level of evidence than English articles identified

B.2. RESULTS OF LITERATURE SEARCH

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart (Figure 1) presents the results of the literature search and the application of the study selection criteria (listed in Box 1 to Box 3) (Liberati et al, 2009).

Studies were selected independently by two reviewers using the Endnote X7 program on the basis of the PICO criteria described in Section A.9. As a quality control measure, a third independent reviewer assessed 10 per cent of the search library using Rayyan software[2], which prioritises articles with title and abstract terms matching the search criteria. Additional articles identified in the quality control step were assessed and considered for inclusion.

When there was doubt regarding the inclusion of an article, the final decision was made through consultation with the second independent reviewer. Studies that could not be retrieved or that technically met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix F. All other studies that met the inclusion criteria are listed in Appendix D.

The search identified 14,171 articles after duplicates were removed, following which assessment of the titles and abstracts led to exclusion of 13,908 the articles. The remaining 269 articles (including six HTAs) were identified as possibly relevant to one or more of the population groups, and full texts were sought for further examination. Of the 269 possible articles, 30 were excluded on the basis of wrong study type (including abstracts), 12 for the wrong population, 45 for the wrong intervention, 12 for the wrong comparator, 31 for the wrong outcome measures, and 1 as it had been retracted. Ten articles that were not in English were excluded as they did not report data of higher level evidence than English articles. The remaining 128 articles were considered 'technical includes' for appraisal.

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[2] Rayyan is a systematic review literature culling tool developed by the Qatar Computing Research Institute: http://rayyan.qcri.org/
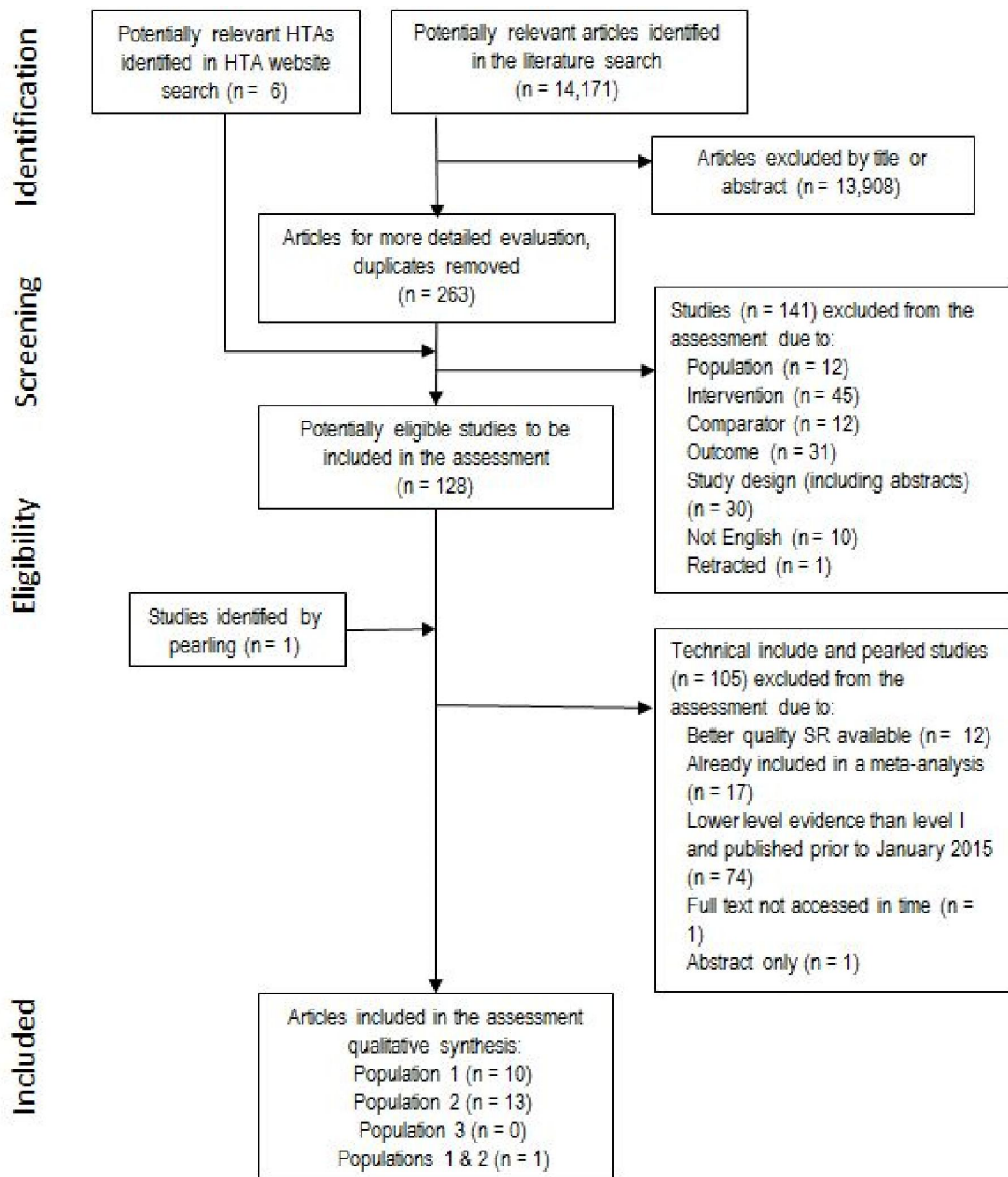
Figure 1   Summary of the process used to identify and select studies for the assessment

A profile of each included study is given in Appendix D (Table 59 to Table 62). This study profile describes the authors, study ID, publication year, study design and quality, study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Sections B.4 and B.5.b.

The evidence was appraised in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews). Some risk of bias items were assessed for the study as a whole (for example, selection bias and publication bias), while others were assessed at the outcome level using GRADE (Grading of Recommendations Assessment, Development and Evaluation; Section B.3) methodology.

Stage 2: Extraction of the prespecified outcomes for this assessment, using a narrative synthesis to assess the consistency of the findings across the included studies, to estimate effect per outcome.

Stage 3: Rating the overall quality of the evidence per outcome, across studies, on the basis of the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence and likelihood of publication bias, to indicated the confidence in the estimate of effect in the context of Australian clinical practice (Appendix E). As systematic reviews (SRs) were included, GRADE was applied, taking into account the individual studies included for each outcome in the SRs, as well as additional comparative data published since the SRs.

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Section B.7).

B.3.   RISK OF BIAS ASSESSMENT

Evidence retrieved from the searches was assigned a level of evidence according to the National Health and Medical Research Council's (NHMRC) Evidence Hierarchy (NHMRC 2000). The NHMRC criteria for interventional research questions are tabulated in Appendix G.

Study quality was evaluated and reported using an appropriate instrument for quality assessment: case series were assessed using the UK National Health Service (NHS) Centre for Reviews and Dissemination (CRD) checklist (Khan et al 2001); randomised controlled trials (RCTs) and comparative observational studies were assessed using the Downs and Black checklist (Downs & Black 1998); and SRs were assessed against the AMSTAR checklist (Shea et al 2007). The level of bias attributed to each study is included in the study profiles in Appendix E, and an overall quality rating was applied.

GRADE methodology was used to assess the risk of bias within the evidence base at an applicable outcome level. An overall risk of bias was estimated for each outcome across studies. GRADE was not applied to the case series discussed in Population 2, and evidence profile tables were not produced; GRADE would have assessed all case series as very low quality, and the way the outcomes were presented in the case series made them unsuitable for assessment as a group.

B.4.   OUTCOME MEASURES AND ANALYSIS

Appendix D gives details of the outcomes measured in the included studies. The outcomes were relatively consistent and relevant. Outcomes such as survival and local tumour progression were measured consistently across studies by imaging tools such as magnetic resonance imaging or ultrasound. A large proportion of studies described the intervention, comparator and imaging techniques. Retrospective studies relied on databases of patient progress to conduct their studies or analysis, but the accuracy of these databases was not described.

As three systematic reviews on this topic were completed in the last year, no separate meta-analyses were conducted. Rather, an overview of the results of the SRs was prepared to compare and contrast the SRs and to look for consistency in their findings. Studies published since the search period of the SRs were also identified to look for results that would be likely to change the findings of the existing SRs (such as RCTs). A small number of these extra studies were identified and their results are also reported, but they were not meta-analysed, as they were very similar to the existing SR results.

POPULATION 1

B.5.A   CHARACTERISTICS OF THE EVIDENCE BASE

Appendix D gives details of the individual studies included in the evidence base. A summary is provided in Table 13.In all, four SRs were included for Population 1. All included RCTs and comparative studies (level II and III evidence) (ASERNIP-S 2006; Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015). Evidence provided by Huo and Eslick (2015) was included in this review for Populations 1 and 2. While the SRs themselves were of moderate to high quality overall in how they were conducted, the studies included in them were predominantly retrospective cohorts with historical comparators, providing only a low level of evidence (level III-3). When outcomes were assessed using the GRADE methodology, they were found to be at high or very high risk of bias, as the retrospective studies were at risk of significant selection bias. Two RCTs (Abdelaziz et al 2014; Shibata et al 2002a) were included across the three latest SRs. As SRs can be afforded the level of evidence of their highest-level included study, the SRs included were all Level I. However, most of the studies within the SRs contributing to meta-analyses were level III-3.

An additional 11 SRs that were potentially relevant were excluded as having poor methodological quality (essentially narrative reviews), or because they included little data on the intervention of interest and contributed nothing to the current assessment, or because they included non-comparative studies. They are listed in Appendix F according to the reason for exclusion.

Of the four included SRs, one was published in 2006, one in 2015 and two in 2016, with the latest literature search ending in July 2015. Three of them were assessed as high quality and one as moderate quality by the AMSTAR tool. All of the SRs provided detailed search and inclusion criteria, and assessed publication bias. The SR by Huo & Eslick was the only one which did not assess the quality of included studies, identify duplicate studies or list excluded studies. Three of the SRs were conducted in Australia (ASERNIP-S 2006; Chinnaratha, M. A. et al 2016; Huo & Eslick 2015) and one in Italy (Facciorusso, Di Maso & Muscatiello 2016). All but one (ASERNIP-S 2006) performed meta-analyses for primary outcomes and conducted statistical analyses of heterogeneity among studies contributing to each outcome (Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015).

Two SRs compared percutaneous MTA and RFA in patients with HCC (Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016), and a third included studies assessing surgical and percutaneous techniques in patients with either HCC or metastatic tumours (Huo & Eslick 2015). The fourth compared RFA with a number of techniques, including MTA, in primary and secondary liver cancer patients (ASERNIP-S 2006). There were five comparative studies in common between three SRs, two of which were also included in the ASERNIP-S review. Together, the four SRs included 19 discrete studies.

Articles published since the search period of the included SRs were also included to ensure that there were no new studies published that would change the results of the SRs (for example, a good-quality RCT).

Three retrospective studies with historical comparators published in 2015 and 2016 were included for their recent evidence (Chinnaratha et al 2015; Lee, KF et al 2016; Potretzke et al 2016). Potretzke et al and Lee et al conducted single-centre studies in the USA and China, respectively. Chinnaratha et al performed a multicentre comparison in Australia. Patients included by Lee et al underwent either laparoscopic or open surgical ablation. The results from this study provide evidence for the questions of safety and effectiveness of *surgical* MTA, in addition to two studies pearled from the SR by Huo and Eslick, which also assessed MTA conducted by these approaches (Sakaguchi et al 2009; Simo, KA et al 2011). These studies were assessed individually to address the question of surgical ablation, as requested by PASC. The level III-2 and 3 studies were all assessed as having moderate or poor quality and moderate to high risk of bias against the Downs and Black checklist.

An additional two studies which assessed complications of MTA and RFA in both Populations 1 and 2 provided evidence for the question on safety (Ding et al 2013; Liang, P et al 2009). Ding et al conducted a retrospective comparison of complications with MTA and RFA in patients with either HCC or metastatic liver tumours; however, metastatic tumours were only a small proportion of the total, so results are reported for Population 1 (level III-2). This study was assessed as moderate quality against the Downs and Black checklist. The study by Liang et al was a large case series (level

IV) looking at complications following liver MTA patients with primary or secondary tumours and was assessed as moderate quality.

Table 13   **Key features of the included evidence comparing MTA with RFA**

Trial/study	K studies[a] N patients	Design and level Duration/recruitment period	Risk of bias	Patient population	Key outcome(s)
Systematic reviews					
Facciorusso et al (2016)	K = 7 N = 774	Level I: SR, MA 1997 to 2013	Low	HCC	Complete response Local recurrence rate Survival Major complications
Chinnaratha et al (2016)	K = 10 N = 1,298	Level I: SR, MA 1997 to 2010	Low	HCC	Local tumour progression Complete ablation Overall survival Major complications
Huo & Eslick (2015)	K = 16 N = 2,062	Level I: SR, MA 1997 to 2013	Moderate	HCC or Met	Overall survival Disease-free survival Local tumour recurrence Complete ablation Adverse events
ASERNIP-S (2006)	K = 5 N = 303	Level I: SR 1997 to 2002	Low	HCC or CRLM	Number of sessions Session time
Non-randomised comparative studies					
Lee et al (2016)	N = 73	Level III-3: RHCC 2003 to 2011	Moderate	HCC	Recurrence-free survival Overall survival Adverse events Procedure related deaths
Chinnaratha et al (2015)	N = 126	Level III-3: RHCC 2006 to 2012	Moderate	HCC	Recurrence-free survival Local tumour recurrence Number of sessions Adverse events
Potretzke et al (2016)	N = 154	Level III-3: RHCC 2001 to 2013	Moderate	HCC	Local tumour progression Overall survival Complications
Ding et al (2013)	N = 879	Level III-2: RCCC 2002 to 2011	Moderate	HCC or Met	Complications Procedure related deaths
Sakaguchi et al (2009)	N = 391	Level III-2: RCCC 1994 to 2005		HCC	Local recurrence Survival
Simo et al (2011)	N = 35	Level III-3: RHCC 2006 to 2008		HCC	Adverse events Procedure related deaths
Non-comparative studies					
Liang et al (2009)	N = 1136	Level IV: case series 1994 to 2007	Moderate	HCC or Met	Complications Procedure related deaths

CRLM = colorectal liver metastases; HCC = hepatocellular carcinoma; K = number of studies; N = number of patients; MA = meta-analysis; Met = metastatic liver tumours; MTA = microwave tissue ablation; RHCC = retrospective historical control cohort; RCCC =

retrospective concurrent control cohort; RFA = radiofrequency ablation; SR = systematic review

^a Applies to systematic reviews only

B.6.A   RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary—Population 1

In patients with unresectable primary liver lesions, what is the safety of percutaneous MTA compared with RFA?

Consistent evidence from four systematic reviews and two large cohort studies found that while the rate of adverse events was lower for RFA than for MTA for most outcomes, the differences were not large enough to be statistically significant, and overall the rates were low, and any differences were unlikely to be clinically significant. One large case series reported that 80.1% of patients undergoing percutaneous MTA experienced pain. Because of the different measures used to assess skin burns, it was difficult to make any conclusion regarding this outcome.

Death associated with either MTA or RFA percutaneous ablation was rare, and there was no difference between groups in mortality rate. However, the studies were underpowered to detect any differences in the rate of rare events.

In patients with unresectable primary liver lesions, what is the safety of open or laparoscopic MTA compared with RFA?

The rate of adverse events in the patients undergoing surgical MTA and RFA reported in two retrospective studies with historical comparators was high but not consistent. The clinical significance of this result is difficult to determine owing to the risk of selection bias in the study designs. Mortality rates were inconsistent in the same two studies and were likely to be confounded by selection bias and patient comorbidities. No conclusive comparisons between MTA and RFA could be drawn.

For patients with primary liver tumours, the large majority of the evidence identified for safety outcomes applied to percutaneous MTA and RFA. Where appropriate, evidence is presented for each outcome separately for included SRs and for primary studies assessing either percutaneous or surgical ablation. In total, three SRs (Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015), one retrospective concurrent control cohort study (Ding et al 2013b), one retrospective case series (Liang, P et al 2009) associated with percutaneous ablation, and two retrospective studies with historical controls for surgical ablation (Lee, KF et al 2016; Simo, KA et al 2011) contributed to evidence for safety outcomes.

Systematic reviews

Three SRs compared the rate of adverse events between patients with HCC undergoing either MTA or RFA (Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015). Facciorusso et al and Chinnaratha et al did not describe or define the major adverse events, but reported ORs for overall adverse events (Table 14). The meta-analyses were consistent in reflecting a more adverse events for MTA than for RFA, but the differences were not statistically significant, and the low rates overall mean that the differences were unlikely to be clinically significant.

Retrospective historical control studies and case series—percutaneous ablation

One concurrent control study (Ding et al 2013b) (level III-2) and one case series (Liang, P et al 2009) (level IV) reported on complications for patients with primary or secondary liver tumours who underwent percutaneous thermal ablation. Both studies were rated as moderate quality. Ding et al investigated 879 patients from one Chinese centre who underwent either RFA or MTA for treatment of HCC (n = 770), CCA (n = 24) or metastatic tumours (n = 85). The data were not reported separately for primary and secondary tumours, but as primary tumours predominated, the study was included here for complications and procedure-related deaths. Liang et al described the complications and deaths associated with MTA in a large Chinese hospital cohort (n = 1157) who underwent the procedure between 1994 and 2007; 77.4 per cent of patients had primary tumours (HCC, cholangiohepatocellular carcinoma and CCA), and data were able to be separated to report here. Both percutaneous and laparoscopic and techniques (85.5 per cent percutaneous for MTA, 81.9 per cent for RFA) were used in the comparative study (Ding et al, 2013), but only percutaneous MTA was used in the larger non-comparative cohort.

The studies reflect similar rates of major complications for MTA, with no difference between groups (Table 14) (GRADE ⊕⊕⊙⊙).

Table 14   Overall major adverse event rates for percutaneous MTA compared with percutaneous RFA in patients with primary liver tumours

Study ID	Risk of bias K studies N patients	MTA n with event/ N (%)	RFA n with event/ N (%)	Relative difference OR (95% CI) Overall effect (Z, P)	Heterogeneity
Systematic reviews					
Chinnaratha et al (2016) Australia	Low K = 7 N = 1043	22/556 (4.0%)	13/487 (2.7%)	0.63 (0.29, 1.38) (favouring RFA)[a] Z = 1.15 (P = 0.25)	Tau^2 = 0.00 X^2 = 2.80, df = 6 (P = 0.83); I^2 = 0%
Facciorusso et al (2016) Italy	Low K = 6 N = 774	NR	NR	1.63 (0.88, 3.03) (favouring RFA) P = 0.12	X^2 = 8.36, df = 6 (P = 0.12) I^2 = 28%
Retrospective concurrent control studies					
Ding et al (2013) (percutaneous ablation)	High N = 879	20/654[b] (3.1%)	13/376[b] (3.5%)	0.88 (0.43, 1.79) P = 0.73 (favouring MTA)[c]	X^2 = 4.19
Case series					
Liang et al (2009) (percutaneous ablation)	High N = 1136	22/879[d] (2.5%)	NA	NA	NA

CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; NR = not reported; OR = odds ratio; RFA = radiofrequency ablation

[a] In the systematic review by Chinnaratha et al, RFA was the intervention and MTA was the comparator, in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator

[b] Total number of ablation sessions

[c] OR and confidence intervals calculated from published data

[d] Total number of patients

This trend was repeated for odds ratios (ORs) for individual adverse events reported in the SR by Huo and Eslick (Table 15) (Huo & Eslick 2015). The OR reflected higher frequency in MTA patients for all outcomes except subcapsular haematomas, for which the OR indicated equivalence between groups. The number of studies contributing data to each outcome varied between two and six. Low event numbers may render the trend towards more adverse events associated with MTA inconclusive. Heterogeneity was low among studies for all outcomes except pain, where there was moderate heterogeneity (I^2 = 61.86 per cent) among four studies contributing to that outcome.

Ding et al (Ding et al 2013b) and Liang et al (Liang, P et al 2009) also reported the number of patients experiencing specific adverse events (Table 15). Pain was by far the most common adverse event in one study: 910 of 1136 patients experienced pain following MTA (80.1 per cent) (Liang, P et al 2009). However, the meta-analysis by Huo and Eslick found no significant difference in pain experienced between MTA and RFA groups (OR 1.70, 95 per cent CI 0.91, 3.19; P = 0.10). Liang et al also reported skin burn that did not require treatment (1.8 per cent of MTA patients). Ding et al reported a skin burn in only one MTA patient, but this was a second degree burn. Other reported adverse events were rare.

The ORs for specific adverse events show a trend that slightly favours RFA; however, serious adverse events were rare overall, and there is unlikely to be any clinical significance in the differences.

Table 15 Rates for individual major adverse events following percutaneous MTA compared with percutaneous RFA in patients with primary liver tumours

Undergoing percutaneous ablation	Study ID *K* studies *N* patients[a]	MTA (%)	RFA (%)	Relative difference OR (95% CI) Overall effect (*P*)	Heterogeneity
Systematic reviews	**Huo & Eslick (2015)**				
Bile duct injury	*K* = 4	NR	NR	1.73 (0.74, 10.13) *P* = 0.65	$I^2 = 0$ (*P* = 0.53)
Liver decompensation	*K* = 2	NR	NR	2.92 (0.43, 19.65) *P* = 0.27	$I^2 = 0$ (*P* = 0.38)
Peritoneal haemorrhage	*K* = 2	NR	NR	3.26 (0.35, 30.05) *P* = 0.30	$I^2 = 0$ (*P* = 0.95)
Pain	*K* = 4	NR	NR	1.70 (0.91, 3.19) *P* = 0.10	$I^2 = 61.86$ (*P* = 0.05)
Subcapsular haematoma	*K* = 5	NR	NR	1.00 (0.29, 3.49) *P* = 1.00	$I^2 = 0$ (*P* = 0.63)
Fever (>38 °C)	*K* = 4	NR	NR	1.21 (0.88, 1.66) *P* = 0.24	$I^2 = 0$ (*P* = 0.49)
Skin burn	*K* = 4	NR	NR	1.20 (0.30, 4.74) *P* = 0.79	$I^2 = 0$ (*P* = 0.53)
Pulmonary effusion	*K* = 6	NR	NR	1.33 (0.7, 2.52) *P* = 0.38	$I^2 = 11.41$ (*P* = 0.34)
Retrospective concurrent control study	**Ding et al (2013)**				
Liver dysfunction	*N* = 879	4 (0.61%)	1 (0.27%)	*P* = 0.66	NA
Liver abscess	*N* = 879	1 (0.15%)	3 (0.8%)	*P* = 0.14	NA
Intractable pleural effusion	*N* = 879	5 (0.76%)	2 (0.53%)	*P* = 1.00	NA
Bile duct injury and biloma	*N* = 879	2 (0.3%)	NR	NA	NA
Skin burns—second degree	*N* = 879	1 (0.15%)	0	NA	NA
Case series	**Liang et al (2009)**				
Liver abscess	*N* = 1136	4 (NR)	NA	NA	NA
Pleural effusion requiring thoracentesis	*N* = 1136	12 (1.0%)	NA	NA	NA
Bile duct injury and biloma	*N* = 1136	3 (0.26%)	NA	NA	NA
Skin burn requiring no treatment	*N* = 1136	21 (1.8%)	NA	NA	NA
Pain	*N* = 1136	910 (80.1%)	NA	NA	NA

CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; NR = not reported; OR = odds ratio; RFA = radiofrequency ablation

[a] Number of patients not provided for individual adverse events reported by Huo and Eslick, 2016

[b] Intractable pleural effusion

[c] Pleural effusion requiring thoracentesis

[d] Second degree skin burn

[e] Skin burn requiring no treatment

Retrospective historical control studies—surgical ablation

The adverse events for surgical ablation are reported separately, as the non-percutaneous approach could contribute to a variation in event numbers. Adverse events were reported in two retrospective studies with historical comparators. One study matched patient characteristics between MTA and RFA groups to compare the two treatments (Lee, KF et al 2016). In this single-centre study conducted in Hong Kong, MTA was used for laparoscopic or open surgical ablation, owing to the size of the microwave antenna in use. Patients who underwent RFA by surgical approach were matched to the MTA group. Lee et al found no statistically significant difference between the two groups in the complication rate, although there were more events in the RFA group (Table 16).

The study by Simo et al included 13 patients who underwent laparoscopic MTA and 22 who underwent laparoscopic RFA. More serious adverse events occurred in the RFA group than in the MTA group, such as pseudomonal urosepsis and multisystem organ failure in one patient and spontaneous bacterial peritonitis in another. The rate of ablation-related complications was higher in the MTA group (8/13, 61.5 per cent) than in the RFA group (10/22, 45.5 per cent) (Table 16).

The adverse event rate is higher for surgical ablation than for percutaneous ablation; however, it is not clear whether reports for the two techniques included similar events. The studies are small and there is a high risk of selection bias in the studies due to the non-randomised study design and historical comparators, so the results may not be reliable (GRADE ⊕⊙⊙).

Table 16   Adverse events for MTA compared with RFA in patients with primary liver tumours undergoing surgical ablation

Study ID	*N* patients	MTA *n* with event/*N* (%)	RFA *n* with event/*N* (%)	Relative difference OR (95% CI) Overall effect (*P*)
Retrospective historical control studies				
Lee et al (2016)	*N* = 73	4/26 (15.4%)	16/47 (34.0%)	0.35 (0.10, 1.20)[a] *P* = 0.09
Simo et al (2011)	*N* = 35	8/13 (61.5%)	10/22 (45.5%)	1.92 (0.47, 7.77)[a] *P* = 0.36

CI = confidence interval; MTA = microwave tissue ablation; OR = odds ratio; RFA = radiofrequency ablation

[a] Odds ratio and *P* value were calculated by the authors of this assessment using the raw data provided in the study

PROCEDURE RELATED MORTALITY

Systematic reviews

Not data were reported for this outcome.

Retrospective concurrent control cohort study and case series—percutaneous ablation

Retrospective cohort studies by Ding et al and Liang et al reported the number of procedure-related deaths. Death rates were low and similar in both groups (Table 17) (GRADE ⊕⊕⊙⊙).

Retrospective historical control studies—surgical ablation

Two retrospective level III-3 studies reported on the 30-day mortality for patients undergoing surgical ablation. Lee et al reported that there were no mortalities in either the MTA or RFA groups at 30 days after ablation in patients undergoing a laparoscopic approach or laparotomy. Simo et al reported three deaths in the RFA group and no deaths in the MTA group at 30 days after ablation in patients undergoing laparoscopic ablation. The size and quality of these studies prevents any conclusions from being drawn from this evidence (GRADE ⊕⊙⊙⊙).

Table 17   Procedure-related deaths for MTA compared with RFA in patients with HCC undergoing percutaneous ablation

Study ID	Risk of bias N patients	MTA n events/ N patients (%)	RFA n events/ N patients (%)	Relative difference OR (95% CI) Overall effect (P)
Retrospective historical control study				
Ding et al 2013	N = 879	2/556 (0.36)%	1/323 (0.31%)	1.16 (95% CI 0.11, 12.87)[a] P = 0.90
Case series				
Liang et al 2009	N = 1136	2/1136 (0.2%)	NA	NA

CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; OR = odds ratio; RFA = radiofrequency ablation

[a] Odds ratio and P value were calculated by the authors of this assessment using the raw data provided in the study

IS IT EFFECTIVE?

Summary—Population 1

In patients with unresectable primary liver lesions, what is the effectiveness of percutaneous MTA compared with RFA?

The evidence from four systematic reviews (level I) and two recent non-randomised comparative studies (level III-3) shows that there was no difference in local recurrence, overall survival (OS), recurrence-free survival or overall complete ablation between percutaneous MTA and RFA in patients with HCC.

Four statistically significant exceptions in favour of MTA were found: local recurrence in a subgroup analysis of patients with tumours outside the Milan criteria in one Level III-3 study; OS at 6 years and disease-free survival at 5 years in one SR; and OS at 5 years in a subgroup analysis of ablation for tumours ≥3.5 cm in one level III-3 study. These results are to be considered with caution, as they go against the trend of the bulk of the evidence, and confounding of the outcomes is likely.

Ablation time favoured MTA over RFA in two SRs, but details are limited, making the result unreliable. One of the SRs also found that MTA required more sessions than RFA, but limited data again make the results unreliable.

In patients with unresectable primary liver lesions, what is the effectiveness of open or laparoscopic MTA compared with RFA?

Three level III-2 and III-3 studies contributed data to the question of open or laparoscopic MTA and RFA. Results mirrored those for percutaneous ablation, in that there were no significant differences between intervention and comparator for local recurrence, OS, complete ablation or recurrence-free survival.

One small level III-3 study found that ablation time and operating time were lower for laparoscopic MTA. The difference in ablation time could have a clinical impact but was not statistically tested. Operating time showed a significant difference. Patients undergoing laparoscopic ablation were more likely to spend less than 1 day in hospital if they underwent MTA. Because of the risk of bias associated with the historical comparator in this study, these results are not conclusive. The clinical impact of these results is difficult to determine.

PRIMARY EFFECTIVENESS OUTCOMES

Effectiveness outcomes are reported separately according to study design and by approach to ablation (percutaneous or surgical) when data are available or where it is considered appropriate. For the purposes of this review, tumour recurrence in association with thermal ablation is defined as regrowth of tumour tissue immediately adjacent to the ablation site. Complete ablation is the absence of residual disease up to approximately 1 month following ablation. Recurrence may be detected through imaging techniques or biopsy analysis within a month following ablation and may lead to further treatment sessions (Lee, KF et al 2016).

Systematic reviews

Three SRs reported on local tumour recurrence following MTA or RFA (Chinnaratha, M. A. et al 2016; Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015) and conducted meta-analyses of the data. The five studies that were common to all three SRs, including the RCT by Shibata et al (2002), reported on local recurrence. Remaining studies in the SRs reporting on local recurrence were all non-randomised comparisons except for that by Abdelaziz et al (2014), in which patients were prospectively assigned to percutaneous MTA or RFA by a random coin toss. This Egyptian study was included in two of the SRs (Facciorusso, Di Maso & Muscatiello 2016; Huo & Eslick 2015). Rather than local tumour recurrence, Chinnaratha et al reported local tumour progression and included the results of an abstract publication by the same authors that was not included in the other two SRs.

Results of the meta-analyses are reported in Table 18. There was no significant difference between MTA and RFA across the three reviews, with ORs (95 per cent CI) of 1.01 (0.54, 1.87) (Facciorusso, Di Maso & Muscatiello 2016), 1.01 (0.67, 1.50) (Chinnaratha, M. A. et al 2016) and 1.17 (0.61, 2.24) (Huo & Eslick 2015). There was moderate heterogeneity among included studies (I^2 = 23 to 56 per cent). Mean follow-up periods were reported by two SRs (5–45 months, Chinnaratha et al, 2016; 10–137 months, Huo & Eslick, 2015); however, the time frame of tumour recurrence was not reported in any study. Similar study inclusions are likely to explain the consistency of ORs for local recurrence among the SRs; and in the two SRs that provided forest plots, none of the individual studies included in the meta-analyses had an OR that was statistically significant, indicating that the individual studies in these SRs were all consistent in finding no difference between the groups.

Facciorusso et al sought to determine whether the heterogeneity among studies affected the OR by conducting a meta-analysis of studies they judged to be high quality. The OR for local recurrence remained non-significant (OR 1.57; 95 per cent CI 0.76, 3.26; *P* = 0.23), although the heterogeneity was reduced (χ^2 = 2.79, df = 2, *P* = 0.25, I^2 = 28 per cent).

Retrospective historical control studies—percutaneous ablation

Two retrospective observational studies with historical comparators provided evidence on local tumour recurrence in patients who underwent either MTA or RFA (Chinnaratha et al 2015; Potretzke et al 2016). These studies were conducted in single- or multi-institute centres that used RFA in earlier years and then transitioned to MTA in 2011 to 2012, and were classified therefore as having historical comparators (level III-3). They were assessed as low to moderate for risk of bias.

The articles by Chinnaratha et al and Potretzke et al reported the local tumour progression at follow-up times between 12 months and 5 years. Results are shown in Table 18. Potretzke et al were the only authors who published hazard ratios (HRs) for this outcome, using two statistical methods. By Cox's method, the HR reached statistical significance, favouring MTA (HR 2.17; 95 per cent CI 1.04,

4.50; P = 0.04). By Fine and Gray's method, however, the trend was the same but statistical significance was not reached (HR 2.07; 95 per cent CI 0.95, 4.26; P = 0.07). There was no significant difference between MTA and RFA in the other two studies. The inconsistency of the results likely reflects heterogeneity among studies, and possible confounding by non-concurrent intervention and comparator groups, and variations in treatment such as improved chemotherapy regimens and technical advancement of equipment (GRADE ⊕⊕⊙⊙).

Retrospective comparative cohort studies—surgical ablation

Three additional retrospective studies with historical or concurrent comparators compared MTA and RFA performed laparoscopically (Simo, KA et al 2011), endoscopically (by laparoscopy or thoracoscopy) (Sakaguchi et al 2009) or surgically (laparoscopy or open surgery) (Lee, KF et al 2016). The articles were assessed as moderate-quality level III-2 (Sakaguchi et al) and Level III-3 studies, and all reported on local recurrence (Table 18). In China, Lee et al reported no significant difference in local recurrence rates for tumours <3.5 cm and ≥3.5 cm in size between MTA and RFA; however, data were based on small event and patient numbers (N = 73). The result was similar when all tumours were considered together.

In the USA, Sima et al reported the number of patients alive with locally recurrent disease at the end of follow-up (0 per cent for MTA and 9.1 per cent for RFA; n = 35). However, the mean follow-up time for the MTA group was shorter (7 months for MTA vs 19 months for RFA), and so results are not easily compared. The largest of the three studies, in Japan (n = 391) (Sakaguchi et al 2009), reported a non-significant relative risk of 0.65 (P = 0.41) for MTA compared with RFA for local recurrence (GRADE ⊕⊙⊙⊙).

Table 18   Local tumour recurrence following MTA compared with RFA in patients with primary liver tumours

Study ID	Risk of bias K studies	MTA n with event/N (%)	RFA n with event/N (%)	Relative difference OR (95% CI) Overall effect	Heterogeneity
Systematic reviews -	**percutaneous**	**ablation**			
Chinnaratha et al (2016) Australia	Low K = 10 N = 1298	84/660 (12.7%)	92/638 (14.4%)	1.01 (0.67,1.50) (favours MTA)[a] Overall effect: $Z = 0.03$ $P = 0.98$	Tau^2 = 0.09 X^2 = 11.70, df = 9 ($P = 0.23$) $I^2 = 23\%$
Facciorusso et al (2016) Italy	Low K = 7 N = 967	62/541 (11.5%)	49/426 (11.5%)	1.01 (0.54, 1.87) Overall effect: $Z = 0.03$ $P = 0.98$	Tau^2 = 0.35 X^2 = 12.30, df = 6 ($P = 0.06$) $I^2 = 51\%$
Huo and Eslick (2015) Australia	Moderate K = 7 N = NR	NR	NR	1.17 (0.61, 2.24) Overall effect: $P = 0.64$	$I^2 = 56$ ($P = 0.04$)
RHCC studies -	**percutaneous**	**ablation**			
Chinnaratha et al (2015) Australia Level III-3	Moderate N = 126 Follow-up NR	6/25 (25.8%)	23/101 (22.8%)	1.13 (NR) $P = 0.7$[b]	NA
Potretzke et al (2016) USA Level III-3	Moderate N = 154 Follow-up NR	12/136 (8.8%)	12/69 (17.4%)	Cox (favours MTA): 2.17 (1.04, 4.50) $P = 0.04$ Fine and Gray (favours MTA): 2.07 (0.85, 4.26) $P = 0.07$	NA
RHCC / RCCC studies -	**surgical**	**ablation**			
Lee et al (2016) Hong Kong Level III-3 (RHCC)	Moderate N = 73	6/26 (23.1%)	12/47 (25.5%)	0.91 (NR) $P = 0.82$[c]	NA
Simo et al (2011) USA Level III-3 (RHCC)	Moderate N = 35	0 (0%)[d]	2/22 (9.1%)[d]	NR	NA
Sakaguchi et al (2009) Japan Level III-2 (RCCC)	High N = 391	NR	NR	RR = 0.65, $P = 0.32$[e]	

CI = confidence interval; df = degrees of freedom; MTA = microwave thermal ablation; NA = not applicable; NR = not reported; RHCC = retrospective historical control cohort; RCCC = retrospective concurrent control cohort; OR = odds ratio; RR = relative risk; RFA = radiofrequency ablation

[a] In the systematic review by Chinnaratha et al, RFA was the intervention and MTA was the comparator, in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator.
[b] Statistical test not reported.
[c] Fisher's exact test.

Subgroup analyses for local tumour recurrence

The three SRs conducted subgroup analyses of local tumour recurrence. Facciorusso et al analysed three studies enrolling patients with high tumour burden. Tumour progression was significantly lower in the MTA group than in the RFA group (OR 0.46, 95 per cent CI 0.24, 0.89; P = 0.02; χ^2 = 0.93). Heterogeneity was low (Facciorusso, Di Maso & Muscatiello 2016) (GRADE ⊕⊕⊙⊙).

In the SR by Chinnaratha et al, local tumour progression was stratified by stage of disease into three categories: very early stage HCC (single tumour ≤2 cm), early stage (Milan criteria; single tumour ≤5 cm or up to 3 tumours ≤3 cm each) and outside Milan criteria (single tumour >5 cm or >3 nodules). The meta-analysis of this final, most severe category gave an OR that reached significance in favour of MTA (OR = 1.88; 95 per cent CI 1.10, 3.23; P = 0.02) (GRADE ⊕⊙⊙⊙), whereas ORs for the other two categories did not reach significance, although they tended to favour RFA (Chinnaratha, M. A. et al 2016). Results are presented in Table 19 (GRADE ⊕⊕⊙⊙).

In a similar finding, Huo & Eslick reported a significant difference between MTA and RFA for the patients whose disease did not fulfil Milan criteria, that is, with more severe disease. The OR favoured MTA (OR = 0.36; 95 per cent CI 0.22, 0.58; P < 0.001) (GRADE ⊕⊙⊙⊙). Further subgroup analysis assessed a number of factors across studies, including brand of machinery, type of tip used, time of ablation and Milan criteria, but no differences were significant (Huo & Eslick 2015).

The two comparative studies also performed subgroup analyses according to size of the tumour. The Chinnaratha et al study compared patients with tumours ≤20 mm and found no statistically significant difference between MTA and RFA groups (10 vs 17 per cent; HR 0.59; P = 0.5) (Chinnaratha et al 2015) (GRADE ⊕⊙⊙⊙). The number of patients or events in each group was not reported. Potretzke et al analysed subgroups of tumour size <3 cm and ≥3 cm and again found no significant difference between MTA and RFA in either category (Potretzke et al 2016) (GRADE ⊕⊙⊙⊙). Despite not reaching significance, results from all categories in the two studies favoured MTA over RFA; however, the studies were of low-level evidence and were rated moderate for risk of bias, and so should be considered cautiously.

In conclusion, three meta-analyses of the subgroup of patients with higher degree of disease severity, variously measured, produced statistically significant results in favour of MTA for local recurrence. It is possible that MTA results in better outcomes for patients with higher severity than RFA. However, as most of the studies contributing to the outcomes have historical rather than concurrent comparators, the results are likely confounded by improvements in other treatments for more severe cancer over time. There is also likely to be selection bias in these studies, with little information about appropriate patient selection or prognostic factors available.

Table 19   Local tumour recurrence by stage of tumour (Chinnaratha et al, 2016)

Subgroup	K studies N patients	MTA n with event/ N (%)	RFA n with event/ N (%)	Relative difference OR (95% CI) Overall effect (Z, P)	Heterogeneity
Very early stage HCC (single tumour ≤2 cm)	K = 2 N = 143	12/75 (16.0%)	5/68 (7.3%)	0.48 (0.15,1.57) (in favour of RFA)[a] Overall effect: Z = 1.21 (P = 0.22)	Tau^2 = 0.00 X^2 = 11.74, df = 1 (P = 0.39) I^2 = 0%
Early stage (Milan criteria; single tumour ≤5 cm or up to three tumours ≤3 cm each)	K = 5 N = 705	45/333 (13.5%)	49/372 (13.2%)	0.73 (0.45, 1.19) (in favour of RFA)[a] Overall effect: Z = 1.26 (P = 0.21)	Tau^2 = 0.00 X^2 = 2.60, df = 4 (P = 0.63) I^2 = 0%
Outside Milan criteria (single tumour >5 cm or >3 nodules)	K = 3 N = 450	27/252 (10.7%)	38/198 (19.2%)	1.88 (1.10, 3.23) (in favour of MTA)[a] Overall effect: Z = 2.30 (P = 0.02)	Tau^2 = 0.00 X^2 = 0.03, df = 2 (P = 0.98) I^2 = 0%
Test for subgroup differences	N = 3 groups	NA	NA	NA	X^2 = 8.32, df = 2 (P = 0.0.02) I^2 = 75.9%

CI = confidence interval; df = degrees of freedom; MTA = microwave thermal ablation; NA = applicable; OR = odds ratio; RFA = radiofrequency ablation

[a] In the systematic review by Chinnaratha et al, RFA was the intervention and MTA was the comparator, in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator

COMPLETE ABLATION

Systematic reviews

Two SRs compared complete ablation rates between MTA and RFA groups (Chinnaratha, M. A. et al 2016; Huo & Eslick 2015). One SR assessed complete response rate (Facciorusso, Di Maso & Muscatiello 2016), described as absence of residual viable tumour in the treated nodule, an equivalent outcome to complete ablation. The SR results were consistent in that all ORs were close to 1, indicating very little difference between MTA and RFA groups, and there was low heterogeneity among included studies for this outcome (Table 20) (GRADE ⊕⊕⊙⊙).

Table 20   Complete ablation for MTA compared with RFA reported in systematic reviews

Study ID	Risk of bias *K* studies *N* patients	MTA *n* with event/*N* (%)	RFA *n* with event/*N* (%)	Relative difference OR (95% CI) Overall effect	Heterogeneity
Systematic reviews—percutaneous ablation	-	-	-	-	-
Chinnaratha et al (2016) Australia	Low *K* = 8 *N* = 1081	510/548 (93.1%)	496/533 (93.1%)	1.03 (0.63, 1.69) (favours RFA)[a] Overall effect: $Z = 0.14$ ($P = 0.89$)	$Tau^2 = 0.00$ $X^2 = 5.13$, df = 7 ($P = 0.64$) $I^2 = 0\%$
Facciorusso et al (2016) Italy	Low *K* = 6 *N* = 887	459/492 (93.3%)	364/395 (92.2%)	1.12 (0.67, 6.07) Overall effect: $Z = 0.43$ ($P = 0.67$)	$Tau^2 = 2.39$ $X^2 = 12.30$, df = 6 ($P = 0.06$) $I^2 = 0\%$
Huo & Eslick (2015) Australia	Moderate *K* = 10 *N* = NR	NR	NR	0.98 (0.85, 1.14) Overall effect: $P = 0.82$	$I^2 = 0$ ($P = 0.04$)

CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; NR = not reported; OR = odds ratio; RFA = radiofrequency ablation

[a] In the systematic review by Chinnaratha et al. RFA was the intervention and MTA was the comparator in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator

Retrospective historical control studies—percutaneous ablation

One non-randomised comparative study assessed the rate of complete ablation (Potretzke et al 2016), reporting that 'all ablations achieved technical success at the completion of the ablation procedure,' with no further details.

Retrospective historical control studies—surgical ablation

One study (Lee, KF et al 2016) reported similar rates of residual disease in the MTA and RFA groups (3.8 vs 6.4 per cent; *P* > 0.999). A second study of patients undergoing ablation either laparoscopically or thoracoscopically reported that one patient (7.7 per cent) in the MTA group and none in the RFA had local residual disease (Simo, KA et al 2011). The small numbers in these studies render the results difficult to apply across the population of interest (GRADE ⊕⊙⊙⊙).

OVERALL SURVIVAL

Systematic reviews

Three SRs reported overall survival (OS) at different follow-up times. Facciorusso et al (Facciorusso, Di Maso & Muscatiello 2016) reported OS at 3 years after ablation, analysing the two RCTs and four non-randomised comparative studies that were common to the meta-analysis by Chinnaratha et al (Chinnaratha, M. A. et al 2016). The latter authors reported OS at 1 and 3 years. Huo and Eslick (Huo

& Eslick 2015) conducted a meta-analysis at years 1 to 6, the latest analysis including the results of only two studies (total N: MTA = 182, RFA = 277). The OS at year 6 was the only result to reach statistical significance, favouring MTA (OR 1.51; 95 per cent CI 1.02, 2.23; P = 0.04). This result was inconsistent with all other follow-up times, when the results were similar between MTA and RFA, and is unlikely to indicate any real advantage for MTA. The increased survival may be a result of chance, especially as this study made multiple comparisons. Results are tabulated for OS at years 1, 3 and 6 (Table 21–Table 23) (GRADE ⊕⊕⊙⊙ for years 1 and 2, ⊕⊙⊙⊙ for year 6).

Retrospective historical control studies—percutaneous ablation

One study compared OS between patients receiving percutaneous MTA and RFA (Potretzke et al 2016): It reported an HR for OS at 48 months favouring MTA but without statistical significance (HR 1.59; 95 per cent CI 0.91, 2.77; P = 0.09).

Retrospective comparative cohort studies—surgical ablation

One level III-3 study reported OS rates at 1, 3, and 5 years for patients undergoing ablation by surgery (Lee, KF et al 2016). The results were similar at all time points, and although statistically non-significant, all results favoured MTA over RFA. Confidence intervals were not reported, and the results should be considered in the light of the small size and moderate quality of this study (GRADE ⊕⊙⊙⊙).

Table 21   Overall survival at year 1 for MTA compared with RFA in patients with primary liver tumours

Study ID	Risk of bias K studies N patients	MTA n with event /N (%)	RFA n with event /N (%)	Relative difference OR (95% CI) Overall effect	Heterogeneity
Systematic reviews -	**percutaneous ablation**				
Chinnaratha et al (2016) Australia	Low K = 4 N = 538	268/288 (93.1%)[a]	227/250 (90.1%)[a]	1.36 (0.73, 2.54)[a, b] Overall effect Z = 0.96 (P = 0.34) (favours MTA)	Tau^2 = 0.29 X^2 = 4.42, df = 3 (P = 0.22) I^2 = 32%
Huo and Eslick (2015) Australia	Moderate K = 7 N = 1088	NR	NR	1.11 (0.36, 3.47) Overall effect: P = 0.85	I^2 = 32% (P = 0.01)

CI = confidence interval; MTA = microwave tissue ablation; NR = not reported; OR = odds ratio; OS = overall survival; RFA = radiofrequency ablation

[a] The inverse of data published is tabulated here for consistency with other OS data. OR was calculated from absolute numbers using MedCalc statistical software online. Actual data published by Chinnaratha et al reflect the number of deaths per group: RFA 23/250 (9.2%) vs MTA 20/288 (6.9%); OR 1.18 (0.46, 3.03) (favouring MTA); overall effect: Z = 0.35; P = 0.73
[b] In the systematic review by Chinnaratha et al, RFA was the intervention and MTA was the comparator, in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator

Table 22   Overall survival at year 3 for MTA compared with RFA in patients with primary liver tumours

Study ID	Risk of bias K studies N patients	MTA n with event/ N (%)	RFA n with event/ N (%)	Relative difference OR (95% CI) Overall effect	Heterogeneity
Chinnaratha et al (2016) Australia	Low K = 4 N = 538	177/288 (61.5%)[a]	164/250 (65.6%)[a]	0.84 (0.59, 1.19)[a, b] Overall effect Z = 0.99 (P = 0.32) (favours RFA)	Tau2 = 0.17 X2 = 6.44, df = 3 (P = 0.09) I^2 = 53%
Facciorusso et al (2016) Italy	Low K = 6 N = 702	240/382 (62.8%)	203/320 (63.4%)	0.95 (0.58, 1.57) Overall effect: Z = 0.19 (P = 0.85)	Tau2 = 0.21 X2 = 11.20, df = 5 (P = 0.05) I^2 = 55%
Huo and Eslick (2015) Australia	Moderate K = 10 N = NR	NR	NR	0.58 (0.32–1.07) Overall effect: P = 0.08	I^2 = 62% (P = 0.02)

CI = confidence interval; MTA = microwave tissue ablation; NR = not reported; OR = odds ratio; OS = overall survival; RFA = radiofrequency ablation

[a] The inverse of data published was tabulated here for consistency with other OS data. OR was calculated from absolute numbers using MedCalc statistical software online. Actual data published by Chinnaratha et al reflect the number of deaths per group: RFA 86/250 (34.4%) vs MTA 111/288 (38.5%); OR 0.76 (0.44, 1.32) (favouring RFA); overall effect: Z = 0.97; P = 0.33.
[b] In the systematic review by Chinnaratha et al, RFA was the intervention and MTA was the comparator, in contrast with the other systematic reviews and this assessment, in which MTA is the intervention and RFA is the comparator

Table 23   Overall survival at year 6 for MTA compared with RFA in patients with primary liver tumours

Study ID	Risk of bias K studies N patients	MTA n with event/ N (%)	RFA n with event/ N (%)	Relative difference OR (95% CI) Overall effect (P)	Heterogeneity
Huo and Eslick (2015) Australia	Moderate K = 2 N = 449	NR	NR	1.51 (1.02, 2.23) P = 0.04	I^2 = 0 (P = 0.86)

CI = confidence interval; MTA = microwave tissue ablation; NR = not reported; OR = odds ratio; RFA = radiofrequency ablation

RECURRENCE-FREE SURVIVAL

Systematic reviews—percutaneous ablation

One SR reported on disease-free survival at follow-up times of 1 to 5 years after ablation (Huo & Eslick 2015). The 5-year disease-free survival was the only one showing a statistically significant difference between MTA and RFA, favouring MTA (OR 0.60, 95 per cent CI 0.39, 0.94; P = 0.03) (Table 24). Two studies contributed to this outcome, which included a total of 353 patients with similar tumour criteria (one tumour ≤5 cm in diameter or Milan criteria: single HCC ≤5 cm or ≤3 tumours <3 cm). The clinical significance of the result is difficult to determine owing to the low-level evidence of the studies (level III-3) (GRADE ⊕⊕⊙⊙).

Table 24   Disease-free survival following percutaneous ablation for MTA vs RFA in patients with HCC (Huo and Eslick, 2015)

Study details	1 year	2 years	3 years	4 years	5 years
K studies *N* patients	*K* = 6 *N* = 668	*K* = 5 *N* = 470	*K* = 5 *N* = 596	*K* = 5 *N* = 596	*K* = 2 *N* = 353
OR (95% CI) Overall effect (*P*)	0.79 (0.56, 1.13) *P* = 0.20	0.85 (0.58, 1.26) *P* = 0.42	1.03 (0.73, 1.45) *P* = 0.99	0.72 (0.50, 1.04) *P* = 0.08	0.60 (0.39, 0.94) *P* = 0.03
Heterogeneity	$I^2 = 0$ (*P* = 0.79)	$I^2 = 0$ (*P* = 0.55)	$I^2 = 2$ (*P* = 0.39)	$I^2 = 34$ (*P* = 0.20)	$I^2 = 0$ (*P* = 0.44)

CI = confidence interval; HCC = hepatocellular carcinoma; MTA = microwave tissue ablation; NR = not reported; OR = odds ratio; RFA = radiofrequency ablation

Retrospective historical control cohort studies—surgical ablation

One retrospective comparative study reported on disease-free survival at 1, 3 and 5 years after ablation (Lee, KF et al 2016). There was no significant difference between MTA and RFA groups the procedures at any follow-up. When the groups were stratified by tumour size (<3.5 cm and ≥3.5 cm), the results were similar (GRADE ⊕⊙⊙⊙).

NEED FOR REPEAT ABLATION

There were no studies included that reported on this outcome.

ACCURACY OF ABLATION MARGINS

There were no studies included that reported on this outcome.

SECONDARY EFFECTIVENESS OUTCOMES

PROCEDURE TIMES AND NUMBER OF SESSIONS REQUIRED

Systematic reviews—percutaneous ablation

Two SRs reported on the time taken for ablation. Huo and Eslick reported that the duration ranged from 1 to 25 min for MTA and from 6 to 25 min for RFA, reflecting that MTA percutaneous ablation may be briefer (Huo & Eslick 2015). The mean time, number and details of studies contributing to this outcome were not reported, and statistical analyses were not conducted.

The ASERNIP-S review reported on the mean time required per ablation session (ASERNIP-S 2006). This outcome was contributed only by Shibata et al, who defined it as the time from skin disinfection to electrode withdrawal. The mean duration was significantly shorter for MTA (33 ± 11 vs 53 ± 16 min; *P* < 0.001).

The ASERNIP-S review also reported the number of treatment sessions required, drawing on only one RCT (Shibata et al 2002a). Patients receiving MTA received significantly more sessions in total

and per nodule (weighted mean difference −1.3 sessions, 95 per cent CI −1.66, −0.94). As this result came from an older study, it is difficult to tell whether the results are still applicable, considering advances in techniques and equipment (GRADE ⊕⊙⊙⊙).

Retrospective historical control studies—surgical ablation

The average ablation time and average operating time were reported in one level III-3 study comparing MTA and RFA performed laparoscopically (Simo, KA et al 2011). The average total ablation time for MTA was 12 min per lesion (8 to 10 min for initial application plus 2 to 4 min for overlap), and for RFA was 25 min per lesion (12 to 14 min for initial application plus 8 to 10 min for overlap).

The difference in average ablation times was reflected in the average operating times for laparoscopic ablation, for which Simo et al reported a statistically significant difference between MTA and RFA. The average operating times were 112 ± 40 min for MTA and 149 ± 35 min for RFA (P = 0.004). There were only 13 patients in the MTA group and 22 in the RFA group, so results for outcomes of ablation times and operating time are not definitive (GRADE ⊕⊙⊙⊙).

LENGTH OF HOSPITAL STAY

Retrospective historical control studies—surgical ablation

The small comparative study by Simo et al reported that the majority of patients were in hospital for less than 1 day (92 per cent of MTA patients and 82 per cent of RFA patients) for laparoscopic ablation (Simo, KA et al 2011) (GRADE ⊕⊙⊙⊙).

RECOVERY TIME

There were no studies included that reported on this outcome.

PATIENT DISCOMFORT

There were no studies included that reported on this outcome. Pain is assessed above on page 33.

QUALITY OF LIFE

There were no studies included that reported on this outcome.

POPULATION 2

B.5.B   CHARACTERISTICS OF THE EVIDENCE BASE

The evidence base for Population 2 was relatively poor. No RCTs were identified. Although in one good-quality SR (Huo & Eslick 2015) included three comparative studies, two of those studies (Correa-Gallego et al 2014; Nicholl et al 2010) would have been excluded from our review as most of the patients also underwent resection. Therefore, one comparative study provided evidence for the effectiveness of MTA in Population 2. One further comparative study had very limited follow-up and only included six patients in the MTA group, so it was not considered further.

Although there wasn't a large body of literature identified for Population 2, much of the research found had to be excluded because the patients in the studies underwent resection simultaneously with their ablation, and therefore were not 'unresectable' as per the PICO criteria. It appears that this group of patients, who likely have more complex disease than patients in Population 1, are more likely to undergo ablation as *part* of their treatment, rather than the sole treatment.

As the body of comparative evidence was small for Population 2, lower levels of evidence were also considered. These studies were all case series ranging from very small to relatively large, all of poor or moderate quality. The outcomes included in these studies also varied considerably.

The included comparative study provided little information on safety outcomes, and as with the effectiveness data, the information in the identified case series was highly variable.

As these studies would all be considered very low quality using GRADE, and because the outcomes were diverse, GRADE was not applied, and evidence tables were not produced for these studies.

B.6.B   RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary—Population 2

In patients with unresectable liver metastases without extrahepatic spread, what is the safety of percutaneous MTA compared with RFA? In patients with unresectable liver metastases without extrahepatic spread, what is the safety of open or laparoscopic MTA compared with RFA?

There is insufficient evidence to determine whether the safety of MTA is comparable to that of RFA, either percutaneously or by open or laparoscopic approach. Patients in Population 2 are likely to have more complex disease and be more unwell, and it is unclear whether the safety profile for Population 1 is applicable to Population 2.

The only comparative study identified provided limited data on complications. The only safety outcome reported was procedure-related mortality, with none identified (Liu et al 2013a).

Given the lack of comparative evidence, case series that reported on complications were also considered. The non-comparative study by Liang et al reported complications for the group of patients with liver metastases undergoing percutaneous MTA (Liang, P et al 2009). Major complications were skin burn requiring resection (*n* = 1), pleural effusion (*n* = 4), liver abscess (*n* = 2) and biloma (*n* = 1). Minor complications were not reported separately for this group. In a similar study by Livraghi et al, major complications in the group with liver metastases included haemothorax (*n* = 1), hepatic haematoma (*n* = 1), biliary stenosis (*n* = 1), jaundice (*n* = 1), peritoneal haemorrhage (*n* = 1), hepatic abscess (*n* = 1), pneumothorax (*n* = 1) and tumoral seeding (*n* = 1) (Livraghi et al 2012). The biliary stenosis and jaundice both occurred in one patient whose MTA was administered in open surgery; the other procedures were all percutaneous. The authors also reported pain and fever as unquantified procedural side-effects. A study by Shimada et al of four approaches to MTA (open, percutaneous, laparoscopic and thoracoscopic) reported complications in the population with metastases; these included abscess (*n* = 2), biliary fistula (*n* = 2) and bleeding (*n* = 2) (Shimada et al 1998). All but one of these patients had open MTA. Alexander et al's 2015 study of 64 patients with a single liver lesion (including some primary) treated most patients with percutaneous MTA, and reported complications such as nausea, pneumothorax, pneumonia and bradycardia in 23.4 per cent; all complications were rated as minor (Alexander et al 2015). The study by Liang et al (2003) of 74 patients with liver metastases undergoing percutaneous MTA reported no severe complications, but over 90 per cent of patients experienced local pain. Minor to moderate pleural effusion was noted in 7 patients, subcapsular bleeding in 2, and skin burns in 3 (Liang, P et al 2003).

The non-comparative study by Liang et al (2014) compared open and laparoscopic MTA in 13 patients with metastatic liver cancer, and reported just one complication, a bile duct dilatation (Liang, PC et al 2014).

No conclusions can be drawn about the relative safety of MTA in Population 2, for either percutaneous or surgical (open or laparoscopic) approaches. As it is likely that the patients in this group have more complex disease and are more unwell than those in Population 1 as their cancer has already spread, without better evidence it is difficult to judge whether the safety profile for MTA in this group would be similar to that in Population 1.

IS IT EFFECTIVE?

Summary—Population 2

In patients with unresectable liver metastases without extrahepatic spread, what is the effectiveness of percutaneous MTA, with or without chemotherapy, compared with RFA, chemotherapy or both? In patients with unresectable liver metastases without extrahepatic spread, what is the effectiveness of open or laparoscopic MTA, with or without chemotherapy, compared with RFA, chemotherapy or both?

Very little evidence for the effectiveness of MTA in patients with unresectable liver metastases was identified. One comparative cohort study (Level III-2) of 89 patients found that local recurrence rate favoured MTA, and this result was likely to be clinically meaningful; however, there were no statistically significant differences between MTA and RFA in the outcomes of complete ablation rate or overall survival (all GRADE ⊕⊕⊙⊙). Survival from years 2 to 5 did favour MTA, but with the small number of patients included, it is difficult to judge whether the difference was clinically meaningful. No comparative information on any secondary outcomes was identified.

To supplement the evidence for Population 2, case series were also considered; these were of poor to moderate quality, and although they provide some information, without a comparator it is impossible to use them to draw conclusions about MTA's performance compared with RFA.

It is probable that ablation is used in conjunction with other treatments in this population; indeed, many studies were excluded because the patients underwent concomitant resection. Isolating the treatment effect of MTA is therefore difficult in practice and in research.

PRIMARY EFFECTIVENESS OUTCOMES

One SR by Huo & Eslick, described in Section B.5.a, also included some separate analyses for metastatic liver cancers (Huo & Eslick 2015). Three comparative studies of liver metastases contributed to the analysis; however, two were excluded for not fulfilling the PICO criteria. These studies (Correa-Gallego et al 2014; Nicholl et al 2010) both included patients who had undergone MTA or RFA, but >85 per cent of patients also received, meaning that they patients were not 'unresectable'. Thus, the combined survival results in the SR were not applicable to this population.

This left one comparative study for inclusion (Liu et al 2013a). This retrospective comparative study with concurrent controls (level III-2) from China included 89 patients, of whom 35 were treated by MTA and 54 by RFA; the choice of ablation was at the discretion of the physician. All patients either had unresectable tumours or refused surgical resection. The results for the primary outcome measures are shown in Table 25. The authors reported that 49 patients had died, 32 of them owing

to hepatic tumour progression, but they did not provide the data by the type of treatment received. There were no statistically significant differences between MTA and RFA in any of the outcomes measured in this study. Results tended to favour MTA, including OS over 2 to 5 years; however, the overall measure of survival was not statistically significant, and the clinical significance of the findings is difficult to judge in this small study (GRADE ⊕⊕⊙⊙).

One other comparative study, not included in the SR, was identified. Its aim was to measure the size of the ablation area rather than any clinical outcomes; it reported on local recurrence, but only at 6 months' follow-up, which was why it was not included in the Huo & Eslick SR (which specified follow-up of at least 1 year) (Hompes et al 2010). Although this study was comparative, in that it had a matched cohort identified from the institution's database, and therefore theoretically represents a higher level of evidence than single-arm studies, it included only 6 patients who underwent MTA. It presented very limited results on clinical outcomes, only briefly mentioning that no perioperative mortality was observed, and one patient in the MTA group had a local recurrence at 6 months. No conclusions can be drawn from this very small, limited study, and it is not considered further.

Table 25   Population 2: efficacy results of retrospective concurrent control cohort study (Liu et al 2013a)

Outcome	Results MTA	Results RFA	Test
Local tumour recurrence	8.6%	20.3%	$P = 0.07$ (χ^2-test)
Distant tumour recurrence	15/35 (42.9%)	30/54 (55.6%)	$P = 0.24$ (χ^2-test)
Overall survival—1 year	82.4%	86.6%	NR
Overall survival—2 years	66.9%	54.8%	NR
Overall survival—3 years	55.8%	44.3%	NR
Overall survival—5 years	44.0%	31.7%	$P = 0.43$ (overall survival) (Kaplan–Meier method, comparisons using log-rank test)
Complete ablation achieved	58/62 (93.5%)	59/70 (84.3%)	$P = 0.094$ (χ^2-test)

MTA = microwave tissue ablation; NR = not reported; RFA = radiofrequency ablation

Non-comparative studies

Several non-comparative studies were identified that were relevant to Population 2. They are summarised for completeness although they represent a lower level of evidence than provided in the comparative study. All of the non-comparative studies were considered Level IV evidence. These studies were all appraised against the NHS CRD Quality Assessment Scale (Khan et al 2001).

A poor-quality study by Liang et al (2003) reported on 74 patients with liver metastases (Liang, P et al 2003). Despite its lack of information about methodology, it reported outcomes in more detail than most other studies. Among the 33 patients that died, the mean survival time was 22.12 months (SD 13.79, median 20.5 months), with a range of 5 to 65 months. Disease-free survival for the entire follow-up period was achieved by 26 patients (35 per cent). The cumulative survival rates were 91.4

per cent at 1 year, 59.5 per cent at 2 years, 46.4 per cent at 3 years, 29 per cent at 4 years and 29 per cent at 5 years. This study also found that survival was significantly better in patients with one or two metastases than in those with three or more, in those with well differentiated tumours than in those with moderate or poor differentiation, in those with moderate differentiation than in those with poor differentiation, and in those with smaller tumours than in those with larger tumours. These findings highlight the impact that different prognostic factors have on outcomes. Ten patients had a regrowth of a treated lesion, 38 had a new lesion at a different site in the liver, 6 had new extrahepatic lesions, and 4 had both intra- and extrahepatic lesions (Liang, P et al 2003).

Several other smaller studies were identified. In the poor-quality study by Ierardi et al (2013), mean disease-free survival was 20.5 months, and recurrence in a treated lesion was observed during follow-up in 3 of the 31 treated lesions (Ierardi et al 2013). Additionally, 6 of the 25 patients (19.3 per cent) developed disease progression. A small medium-quality study of 18 patients with liver metastases from nasopharyngeal cancer by Li et al (2013) reported complete necrosis in all treated lesions (Li, X et al 2013). Median survival in this group of patients was 41.4 months, and median progression-free survival was 37.5 months. At the last follow-up point, 15 patients were still alive with no signs of progressive metastatic disease. A moderate-quality study of 20 patients included 5 patients with hepatocellular cancer (Martin, Scoggins & McMasters 2007). Many of the patients also had surgical procedures, including resection in 7 and other abdominal surgery in several others. After a median follow-up of 19 months (range 5–23 months), this study reported 1 ablation recurrence and 8 new liver recurrences. A very small poor-quality study examined only 8 patients, and reported that 5 of them were alive with new metastatic foci after a mean observation period of 25.9 months (Abe et al 2005).

Several case series included patients with primary and secondary cancers; where data could be extracted for just Population 2, it has been included here. The moderate-quality study by Alexander et al (2015) included 39 patients, and reported the 1-year likelihood of recurrence as 45.7 per cent in those with CRC metastases, and 70.8 per cent in those with other metastases (Alexander et al 2015). The median cancer-specific survival was 36.3 months for patients with CRC metastases, and 13.9 months for those with other metastases. Median all-cause mortality was 36.3 months for CRC metastases and 10 months for other metastases. The patients with CRC metastases had significantly longer survival times than those with other metastases. An additional moderate-quality study included a relatively large number of patients (*n* = 307, with 653 lesions) (Yu et al 2015). This study was concerned with local tumour progression, and found that 27 of the 653 lesions had local recurrence. Among these recurrences, 20 occurred within 1 year, 6 between years 1 and 2, and 1 after year 2. The local tumour progression rates were 9.8 per cent at 1 year, 15.4 per cent at 2 years and 17.0 per cent at 3 years.

Li et al (2012) investigated patients undergoing MTA with the intention of comparing treatment between lesions close to the diaphragm and those further away; some relevant data was available (Li, M et al 2012). This moderate-quality study included 61 metastatic tumours in 49 patients. The

only outcomes reported were complete ablation, which was achieved in 93.3 per cent of patients, and local tumour progression, in 31.1 per cent of treated tumours. A small, poor-quality case series from Taiwan included 13 patients with CRC metastases (Liang, PC et al 2014). This study included larger tumours (mean size 5.31 cm), and reported complete ablation in 76.9 per cent of patients, with local recurrence in 3 patients and a distant recurrence in 1 patient.

Overall, the general poor quality of the case series, the likelihood of serious selection bias and the considerable variation in the reporting of the limited outcomes make it difficult to draw any conclusions about the effectiveness of MTA from these studies.

POPULATION 3

B.5.C—B.6.C   CHARACTERISTICS OF THE EVIDENCE BASE AND RESULTS

Summary: In patients with unresectable neuroendocrine liver lesions with extrahepatic spread refractory to somatostatin analogues requiring palliative treatment for secretory syndromes, what are the safety and effectiveness of percutaneous, open or laparoscopic MTA of liver tumours compared with RFA, chemotherapy, chemoembolisation, radioembolisation or radiolabelled somatostatin analogue therapy?

There was no evidence identified for the safety and effectiveness of MTA in Population 3. No conclusions can be drawn.

Very little information pertaining to the population with neuroendocrine liver lesions was identified; none was considered suitable for inclusion. A separate search was conducted in PubMed and EMBASE to ensure that the search strategy had identified relevant studies. The search used a simple 'neuroendocrine AND microwave' strategy. No additional studies were identified.

No studies reporting on the safety of MTA in Population 3 were identified.

Two small case series examined MTA in Population 3, but most patients also underwent hepatectomy, or the results were not separately reported, so it is not possible to discern the effect of the MTA (Martin, Scoggins & McMasters 2010; Mayo et al 2010). Another case series (Groeschl et al 2014) that examined MTA-treated patients with neuroendocrine liver metastases, among other liver tumours, excluded patients who underwent the procedure for non-curative intent; thus, it was not the correct population, as treatment in Population 3 is specifically for palliation. One other study, a case series of six patients, was published in Chinese; the abstract reported limited outcomes, including a 'technique effective rate' of 92.9 per cent (not defined) and the reoccurrence of one lesion 3 months after ablation (Qi et al 2012). No conclusions can be drawn from these data.

There is no evidence with which to assess the safety and effectiveness of MTA in Population 3.

B.7 INTERPRETATION OF THE CLINICAL EVIDENCE

On the basis of the evidence profile (summarised in Table 26), it is suggested that, **relative to RFA, MTA has non-inferior safety and non-inferior effectiveness in patients with unresectable primary liver lesions.**

In patients with unresectable metastatic liver disease without extrahepatic spread, there is limited evidence to suggest that, relative to RFA, MTA has non-inferior safety and non-inferior effectiveness.

In patients with unresectable neuroendocrine liver lesions with extrahepatic spread refractory to somatostatin analogues requiring palliative treatment for secretory syndromes, there is no evidence on which to base an assessment of the safety and effectiveness of MTA relative to RFA, chemotherapy, chemoembolisation, radioembolisation, radiolabelled somatostatin analogue therapy or resection.

A relatively large body of recent SR (Level I) evidence, containing 19 individual studies, was consistent in finding no statistical or clinical differences in health outcomes between people with unresectable primary liver lesions undergoing MTA or RFA. Across the primary outcomes of local tumour recurrence, complete ablation and survival, and for adverse events, the SRs consistently reported no differences between the treatments, with infrequent exceptions likely to be statistically significant by chance. Most of the evidence was for percutaneous ablation; the three historically controlled cohort studies of surgical approach also found few differences between MTA and RFA in the reported primary outcomes.

What is interesting about this body of evidence is the lack of RCT evidence informing it. Only two RCTs are included in the SRs, and one of those is an early study (2002). Despite there obviously being a considerable amount of research on MTA, there has been a distinct lack of good-quality research in which selection and performance bias are minimised. This brings the whole body of evidence into question, and is reflected in the low GRADE assessments.

There are several issues with the methodological quality of this evidence base. Firstly, although the studies describe the inclusion criteria and generally have some description of the cancer stages, tumour sizes and number of lesions, there is little other prognostic information available, such as other treatments that have been received or are received during follow-up or time since diagnosis. If studies were larger and randomised, one may expect that these prognostic factors would be balanced between groups, but as most of these studies are small and not randomised, there is likely to be confounding from these prognostic factors. Other important limitations relate to the use of historical control groups in so many studies. It is highly likely that there is bias affecting the selection of patients into non-concurrent cohorts. Not least, there have been improvements in imaging and surgical techniques over time that could affect patient selection for both surgery and ablation, resulting in changes in parameters used to define a patient's status as 'unresectable'. Additionally, treatments for cancer other than ablation change over time, and this could affect survival. Indeed,

ablative treatment itself can change over time, especially as operators become more experienced and image guidance improves.

Little data was identified for Populations 2 and 3. The limited comparative evidence (one study) available for Population 2 echoed that for Population 1, finding no statistically significant differences in effectiveness between MTA and RFA. Although the results tended to favour MTA, it is difficult to judge the clinical significance of these differences. No evidence was found for Population 3.

Populations 2 and 3 are likely to comprise patients with more complex disease, requiring more complex treatment, and this is reflected in the research in which patients underwent MTA with resection. Teasing out the impacts of MTA alone is therefore difficult in these populations.

Overall findings for the critical outcomes of this assessment are presented in Table 26.

Table 26   Balance of clinical benefits and harms of MTA, relative to RFA, and as measured by the <u>critical</u> patient-relevant outcomes in the key studies for Population 1

Outcomes	Studies	Quality of evidence (GRADE)[a]	Range of results: OR /HR and 95% CI, *P*-value	Comments
Local tumour recurrence—percutaneous	3 SRs 3 RHCC	⊕⊕⊙⊙	ORs between 1.01 (0.67, 1.50) and 1.17 (0.61, 2.24) ORs between 0.91 and 1.13 (95% CI not reported) HR 2.17 (1.04, 4.50), *P* = 0.04	No difference between groups
Local tumour recurrence—surgical	3 RHCC 1 RCCC	⊕⊙⊙⊙	MTA 0%–23% vs RFA 9.1%–25.5% with events	No difference between groups
Overall survival 1 year	2 SRs	⊕⊕⊙⊙	ORs between 1.11 (0.36, 3.47) and 1.36 (0.73, 2.54)	No difference between groups
Overall survival 3 years	3 SR	⊕⊕⊙⊙	ORs between 0.58 (0.32,1.07) and 0.95 (0.58, 1.57)	No difference between groups

Recurrence-free survival:
 	
    1 year
    3 years
    5 years
	1 SR
	N = 668
	N = 596
	N = 353
		⊕⊕⊙⊙	
			
			OR 0.79 (0.56, 1.13), *P* = 0.20
			OR 1.03 (0.73, 1.45), *P* = 0.99
			OR 0.60 (0.39, 0.94), *P* = 0.03
				No difference between groups except at 5 y

Complete ablation—percutaneous	3 SR	⊕⊕⊙⊙	ORs between 0.98 (0.85, 1.14) and 1.12 (0.67, 6.07)	No difference between groups
Major adverse events—percutaneous	2 SRs 1 RCCC	⊕⊕⊙⊙	OR 0.63 (0.29,1.38); MTA was reference category OR 1.63 (0.88,3.03), *P* = 0.12 OR 0.88 (0.43, 1.79), *P* = 0.73[b]	No difference between groups; low event rates
Major adverse events—surgical	2 RHCC	⊕⊙⊙⊙	ORs between 0.35 (0.10, 1.20), *P* = 0.09, and 1.92 (0.47, 7.77), *P* = 0.36[b]	No difference between groups; small studies
Procedure-related deaths—percutaneous	1 RCCC	⊕⊕⊙⊙	OR 1.16 (0.10, 12.87), *P* = 0.90[b]	No difference between groups; very low rates

CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HR = hazard ratio; MTA = microwave tissue ablation; RHCC = retrospective historical control cohort; RCCC = retrospective concurrent control cohort; OR = odds ratio; RFA = radiofrequency ablation; SR = systematic review

[a] GRADE Working Group grades of evidence (Guyatt et al 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[b] ORs and CIs calculated from published figures.

SECTION C   TRANSLATION ISSUES

C.1.   OVERVIEW

The clinical data presented in Section B, where relevant and appropriate, were incorporated into the related economic analyses, without quantitative translation. The applicability of data is discussed under the 'Inputs' section of the relevant analysis. Thus, there are no translation studies to present.

SECTION D   ECONOMIC EVALUATION

D.1.   OVERVIEW

From the available evidence, the clinical evaluation suggested that, relative to RFA, the MTA has:

- **non-inferior safety** and **non-inferior effectiveness** (summarised in Table 26) in patients with unresectable primary liver lesions (Population 1)

- **non-inferior safety** and **non-inferior effectiveness** (limited evidence) in patients with unresectable metastatic liver disease without extrahepatic spread (Population 2)

- uncertain safety and uncertain effectiveness (no evidence found) in patients with unresectable neuroendocrine liver lesions with extrahepatic spread refractory to somatostatin analogues requiring palliative treatment for secretory syndromes (Population 3).

On the basis of the clinical conclusions, it is appropriate to assume that overall health-economic outcomes would essentially be the same for both MTA and RFA. Therefore a cost-minimisation approach is appropriate for the economic evaluation.

D.2.   POPULATIONS AND SETTINGS

The populations modelled are Populations 1 and 2 of those groups proposed to be eligible for MTA treatment of liver lesions as discussed in Sections A.4 and D.1. There was inadequate evidence available to support an economic analysis in Population 3.

In the Australian setting, percutaneous MTA is delivered in radiology departments by an interventional radiologist. Intraoperative MTA is performed in conjunction with liver surgery by the surgeon or an interventional radiologist in the operating theatre.

MTA is performed in both private and public hospitals within Australia and usually requires an overnight stay. In the analysis, the procedures provided on a same-day basis are considered as outpatient procedures and those which require an overnight stay are assumed to be inpatient procedures.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

The key characteristics of the economic evaluation are summarised in Table 27.

Table 27   Summary of the economic evaluation

Perspective	Australian healthcare
Comparator	Radiofrequency ablation
Type of economic evaluation	Cost-minimisation
Sources of evidence	Systematic review, sections B.5.a–6.a, B.5.b–6.b
Outcomes	Cost per patient
Methods used to generate results	Cost comparisons
Software package used	Microsoft Excel 2013

D.3.1 LITERATURE REVIEW

A systematic review of cost-effectiveness articles relating to MTA compared with RFA was performed using the PubMed and EMBASE databases. Search strategies relating to literature search outputs from these databases are presented in Table 66, Appendix H. The systematic search resulted in 163 unique articles. None of the identified studies provided relevant information on the cost-effectiveness of MTA compared with RFA in the target populations with unresectable liver lesions.

One prospective phase II study (*N* = 100) was found in the grey literature search that compared the variable direct and fixed direct charges of MTA and RFA in a matched-pair evaluation of patients who were treated for hepatic tumours (Martin, Scoggins & McMasters 2010). Patients were matched by sex, age, histology, number of tumours, size of tumours, operative exposure, and the lack of need for additional concomitant hepatectomy or extrahepatic organ resection. The study reported significantly shorter ablation (median [range]: 13 [5–45] min for MTA, 40 [20–65] min for RFA) and operating times in the MTA group that led to significant improvements in operating room charges, variable direct charges and fixed direct charges for MTA (*P* = 0.02). The associated median [range] procedural costs were estimated to be US$14,812 [$8,958–$20,184] for MTA and US$29,377 [$22,027–$46,043] for RFA. Only 38 per cent of the patients underwent ablation alone, while 53 per cent had concomitant hepatectomy, and 68 per cent had open procedures. Hence, the study population is not relevant to the target populations, as it included more than half of the patients who were amenable to resection. Also, as it was conducted in the USA, the healthcare costs are unlikely to be applicable to the Australian context.

D.3.2 STRUCTURE OF THE ECONOMIC EVALUATION

For Population 1, RFA is identified as a valid comparator to MTA. For Population 2, MTA with or without chemotherapy is compared with RFA with or without chemotherapy.

For both populations, the comparative evidence did not identify a significant difference in outcomes, and justified the assumption that health outcomes would be equivalent across each arm of the economic evaluation. Therefore, the aim of the economic evaluation was to calculate the cost of providing MTA compared with RFA in Population 1, and MTA with or without chemotherapy compared with RFA with or without chemotherapy in Population 2, and present this as a cost-minimisation approach.

D.3.2.1 Outcomes

The clinical evidence in Section B.6 suggests that there are no statistically significant differences in the primary health outcomes (such as local tumour recurrence, complete ablation rate, and OS) associated with MTA and RFA in either population. Neither was evidence identified relating to interim health outcomes such as recovery time or patient discomfort in either population. Therefore, economic outcomes are assumed to be equivalent and are not modelled, as per a cost-minimisation approach.

D.3.2.2 Costs

The applicant claims that MTA has faster ablation times of 4–6 min, in contrast to 10–20 min for RFA, which would result in less time overall spent in the radiology suite, and which may affect the cost of the procedure (MSAC 2016). The applicant proposed graduated fees for MTA based on the number of lesions treated ($1300 for ablation of 2–3 lesions, $1600 for ablation of 4–5 lesions and $2000 for ablation of >5 lesions). PASC advised that graduated fees for up to five lesions should be considered in the assessment (MSAC 2016). The base-case analysis considers the same MBS fee for MTA as for RFA[3]. Economic analyses based on the proposed stratified fee are provided in Appendix I.

Limited evidence suggested that more sessions would be required for MTA (detailed in Section D.4.4). On the contrary, some clinical opinion suggested that fewer sessions are required[4]. Therefore, the base case analysis assumes that the same number of sessions would be required regardless of technique; however, the impact of fewer and more ablation sessions per patient is explored in the sensitivity analysis. As per the clinicians' advice, there are no differences in the after-care or post-ablation patient management between RFA and MTA procedures[4].

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[3] This approach was confirmed with Department of Health (email communication on 4 August 2016) following conclusion of non-inferiority on the basis of clinical evidence.

[4] Email communication with the clinical expert panel; responses from [BK, CT and CR] received on 12, 18 and 19 July 2016.

D.3.2.3   Calculation approach

A stepped approach is taken where the cost of the procedure alone is compared first, and then the cost of other healthcare resources associated with the procedure are added. As the evidence related to the comparative effectiveness of MTA and RFA is limited or inconclusive, various sensitivity analyses are presented for both populations.

D.3.2.4   Assumptions in the economic analysis

- Preoperative and postoperative follow-up costs and procedures are considered similar and are not included in the assessment.

- No statistically significant differences were identified in the adverse event rates across the two procedures (see Section B.6), and are therefore not included in the analysis.

- The comorbidities and their associated impact on perioperative and postoperative patient management are similar and are therefore not incorporated in the analysis.

D.4.   INPUTS TO THE ECONOMIC EVALUATION

D.4.1 RATIO OF INPATIENT AND OUTPATIENT SERVICES FOR RFA AND MTA

Data to estimate the proportion of outpatient RFA services performed for primary HCC were obtained from the Department of Health (see Table 39, Section E.2.a, for further details). Forty per cent of percutaneous RFA procedures were estimated to be outpatient procedures. However, the clinical advice suggested that 80 to 100 per cent of the ablation procedures would require an overnight stay for observation and, if necessary, pain relief, conditional on patients' medical factors.

As the costs associated with an overnight stay exceed the cost of day surgery, a split of 60:40 per cent (inpatient : outpatient) is used in the base-case analysis, and splits of 80:20 and 100:0 are also assessed in the sensitivity analyses for Population 1 with primary liver cancer. In Population 2, it is assumed that patients by definition have advanced (metastatic) disease, and therefore the generalisation is made that all patients will be observed overnight.

D.4.3 RATIO OF PERCUTANEOUS AND INTRAOPERATIVE ABLATION PROCEDURES PERFORMED IN AUSTRALIA

The proportions of percutaneous and laparoscopic/open RFAs performed were derived from the data obtained from MBS statistics online.[5] Approximately 86 to 98 per cent of RFAs were performed percutaneously in private hospitals over the years 2011–2015 (row E/G in Table 37, Section E.2.a).

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[5] Medicare Australia Statistics; <www. medicarestatistics> accessed on 25 July 2016.

D.4.4 Number of Sessions Performed per Patient for Both RFAs and MTAs

The number of sessions required per patient for RFA was estimated from the statistics obtained from the Department of Health; they equated to an average of 1.1 sessions per patient for percutaneous RFA and 1.2 for laparoscopic/open RFA. Equivalent data for MTA services could not be obtained.

Two studies (Shibata et al 2002 and Ohmoto et al 2008, cited in Huo and Eslick 2015) identified during the clinical evaluation reported that the number of treatment sessions per nodule was significantly higher for patients undergoing MTA than RFA (1.1 vs 2.4; $P < 0.001$ in Shibata et al, and 1.7 vs 2.6 in Ohmoto et al). In contrast, the clinical experts suggested that the sufficient ablation with MTA is achieved in one session and it is rare to require another session.[6] The study by Shibata et al was published in 2002; therefore, results may not still be applicable, considering advances in techniques and equipment.

The base-case economic analysis, therefore, assumes that both RFA and MTA achieve complete ablation in one session per patient. Given that the figures from the Shibata et al study for RFA are similar to what are found in the Australian data, these are used in sensitivity analyses to assess the impact of the need for more sessions per patient (Section D.6).

D.4.5 Costs Associated with the Procedures

Resource use and MBS item numbers to be considered in the economic analysis were identified in the protocol (MSAC 2016). The estimated costs associated with MTA and RFA were taken from a number of sources. These included the Medicare fee, Australian Refined Diagnostic Related Group (AR-DRG) (v 7.0 round 18—Public), manufacturer's costs and median charged Medicare fee. The capital costs of RFA and MTA (generator, trolley and applicator) are not included in the analysis.

D.4.5.1 Cost of procedure

The applicant has proposed a graduated fee for MTA services based on the number of lesions treated. However, on the basis of the non-inferiority conclusion, it was advised that funding for MTA should be consistent with RFA[7]. The current funding for RFA is determined by the scheduled fees for MBS items 50950 and 50952, both of which are currently set at \$817.10 per service.

Economic analyses incorporating the suggested stratified MTA fees for proposed populations are presented in Appendix I. Results of these analyses are summarised in Section D.5.

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[6] Email communication with the clinical expert panel; responses received on 12, 18 and 19 July 2016.

[7] Commonwealth feedback to the draft report for MSAC Application 1402. Email communication received from the Department of Health on 4 August 2016.

D.4.5.2   Anaesthesia

Both RFA and MTA procedures involve the use of general anaesthesia. The costs associated with anaesthesia include the costs of the initial consultation with an anaesthetist, anaesthesia management and the anaesthetic drug[8].

The scheduled fees for MBS items 17610 (a brief pre-anaesthesia consultation, less than 15 min, by an anaesthetist) and 21922 (initiation of management of anaesthesia, 7 basic units) are included as costs associated with anaesthesia. Although not specific to ablation procedures, these item numbers were identified as the most applicable ones in the protocol (MSAC 2016).

The fees which anaesthetists charge vary considerably. A part of this fee will be reimbursed by Medicare and some will be reimbursed by the private health insurer. The gap between the amount reimbursed and the fees charged is paid by patients. The cost of anaesthesia management is determined by the number of basic units used, which is based on the time the patient is managed under anaesthetic, and is reliant on the patient's medical conditions and the associated complexities. Currently the MBS rate for one 'Anaesthesia Basic Unit' is $19.80, and the Australian Medical Association values it at $79[9].

In the base case, there is no incremental difference in costs between anaesthetic use for MTA and RFA. However, considering the applicant's claim of faster ablations with MTA, a sensitivity analysis is presented in Section D.6 using the lower number of anaesthesia basic units used for MTA.

D.4.5.3   Other healthcare costs

Other costs associated with both MTA and RFA procedures may include costs of disposable probes, operating or radiology rooms, supplies, pharmaceutical costs, nursing, imaging and hospital stay.

The cost associated with imaging is included in the MBS item descriptors for both MTA and RFA. The protocol mentions that the cost of disposable probes used in MTA was provided by the applicant ($2,960), whereas the cost of disposable probes used in RFA was taken from the 2003 MSAC report (MSAC 2003) and was in the range $1,700–$2,700 (MSAC 2016). The current costs of disposable probes for RFA could not be identified. The costs of these consumables are considered as part of other associated hospitals costs and are not accounted separately.

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[8] Clinical advice was that the anaesthesia provided depends on the treating attending anaesthetist, but in general, total continuous infusion (remifentanil, propofol) or volatiles (sevoflurane or desflurane) are used. The average cost of anaesthetic drug per procedure is assumed to be included in the average pharmacy cost component of the relevant AR-DRG (Independent Hospital Pricing Authority (IHPA) 2015b).

[9] Source: http://hallanaesthesia.com.au/fees-explained/anaesthetist-decide-charge-basic-unit/; accessed on 28 July 2016.

Micro-costing of all other resources used is not possible owing to the limitations of the available data and inter-state and inter-hospital variations in the pricing structure. The most reliable source for estimating hospital costs is the average cost of AR-DRG associated with a particular procedure provided by National Hospital Cost Data Collection (NHCDC). There is no AR-DRG assigned for ablation procedures, and AR-DRG H05B (Hepatobiliary Diagnostic Procedures without Catastrophic Complications) was identified as most applicable for MTA and RFA.

The average costs for AR-DRGs vary across the public and private hospitals. For private hospital costs, reports from NHCDC for Australian private hospitals were sought. The National Efficient Price for private hospitals was last published in NHCDC cost reports, Round 13 (2008–09) (Department of Health 2012). The recent NHCDC cost reports for private hospitals (Independent Hospital Pricing Authority (IHPA) 2015a) provide only cost weights associated with each AR-DRG. The actual average costs of these procedures could not be determined from the data. The average costs per AR-DRG along with the cost weights for private hospitals were last published in NHCDC AR-DRG version 5.1 Round 13 (2008–2009) (Department of Health 2012) and may not still be applicable.

In the base-case analysis, the average cost of AR-DRG H05B (excluding the costs associated with medical and imaging services which are incorporated as MBS fees) from the public hospitals cost report (Independent Hospital Pricing Authority (IHPA) 2015b) is used. An economic analysis using the private sector costs for 2008–09 is presented as additional information in Appendix H (Table 67– Table 70). The costs used in the analysis are adjusted for inflation over time (2016 AUD).[10]

D.4.5.4   Chemotherapy

Population 2 includes treatment with RFA or MTA with or without adjuvant chemotherapy. Data from the South Australian clinical registry for metastatic CRC showed that around 53 per cent of patients received chemotherapy treatment (Neo et al 2011).

No evidence was found for the relative usage of chemotherapy, and the base-case analysis assumes no difference in usage. However, one consultant suggested that MTA may reduce chemotherapy usage by 10 per cent compared with RFA, so this is tested in the sensitivity analysis. The base-case analysis assumes no difference in chemotherapy usage.

The weighted cost of chemotherapy is calculated as the average cost per DRG for AR-DRG R63Z (Chemotherapy), adjusted for inflation[10] (Independent Hospital Pricing Authority (IHPA) 2015b) ($1,518), and multiplied by the proportion of people having chemotherapy (53 per cent).

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[10] Costs converted using Consumer Price Index (CPI) Inflation Calculator of Australian Bureau of Statistics <www.abs.gov.au/websitedbs/d3310114.nsf/home/Consumer+Price+Index+Inflation+Calculator>; accessed on 28 July 2016.

Table 28 summarises the costs associated with MTA and RFA used in the economic analysis.

Table 28   Costs associated with procedures used in the base-case economic evaluation

Item description	MTA	RFA	Source
MBS fees	-	-	-
Ablation procedure	$817	$817	Scheduled fee of MBS items 50950 & 50952
Pre-anaesthesia consultation	$43	$43	Scheduled fee of MBS item 17610
Initiation of management of anaesthesia	$139	$139	Scheduled fee of MBS item 21922
Other healthcare costs	-	-	-
Other hospital costs	$6,236	$6,236	Average cost of AR-DRG H05B[1]
Weighted cost of chemotherapy	$805	$805	Average cost of AR-DRG R63Z × 53%

[1] Average cost of AR-DRG H05B (excluding medical and imaging costs) adjusted for inflation (2016 AUD) using CPI inflation calculator.

Source: MBS and NHCDC Public Hospital Cost Reports (Independent Hospital Pricing Authority (IHPA) 2015b)

AR-DRG = Australian Refined Diagnostic Related Group; CPI = Consumer Price Index; MTA = microwave tissue ablation; MBS = Medicare Benefits Schedule; RFA = radiofrequency ablation

POPULATION 1

D.5.A RESULTS OF THE ECONOMIC EVALUATION

When only the procedural costs of MTA and RFA are compared (excluding all other associated anaesthetic and other healthcare costs), there is no incremental cost associated with MTA in the base case (Table 29).

Table 29   Incremental cost of MTA excluding other associated costs, Population 1

Item description	MTA	RFA	Incremental cost
Ablation procedure	$817	$817	**$0**

MTA = microwave tissue ablation; RFA = radiofrequency ablation

When all other associated healthcare costs are included in the analysis, the cost of both MTA and RFA is estimated to be $7,235. Since in the base case the use of all associated healthcare resources is considered similar across the two procedures, the incremental cost remains the same (that is, $0).

Table 30 shows the overall costs and the incremental cost per patient as calculated for the intervention and comparator in the analysis, with the base-case assumptions.

Table 30   Costs associated with MTA and RFA, Population 1

Item description	MTA	RFA
Ablation procedure	$817	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Other hospital costs	$6,236	$6,236
Total	**$7,235**	**$7,235**
Incremental cost per patient	-	**$0**

Source: Table 28; MTA = microwave tissue ablation; RFA = radiofrequency ablation

D.6.A SENSITIVITY ANALYSES

Sensitivity analyses are presented in Table 31 to assess the impact of varying the costs associated with the procedures. The base-case analysis considered similar costs for MTA and RFA. A sensitivity analysis considering the weighted cost of MTA based on the number of lesions treated per patient ($817 for treating up to 3 lesions, and $1,300 for >3 lesions) was performed. Approximately 70 per cent of the patient population with primary liver cancer is estimated to have one to three lesions (see Table 72, Appendix I). The weighted cost of MTA based on a 70:30 per cent stratification equates to $962.

MTA and RFA are similar procedures with similar safety and effectiveness (Section B). As such, the base-case analysis included similar hospital costs for both. However, as per the applicant's and some clinicians' suggestions, if MTA allows faster ablation times than RFA, this would result in cost savings associated with operating/procedure rooms. The operating costs per unit of time could not be identified from the available data, so sensitivity analyses assuming an arbitrary decrease of 10 and 20 per cent in hospital costs associated with MTA are presented. Also, the number of anaesthesia basic units used is decreased from 7 in the base case (MBS item 21922) to 6 and 5, reducing the cost of management of anaesthesia.

Sensitivity analyses were also performed to assess the impact of varying the number of MTA or RFA sessions per patient, as discussed in Section D.4.4.

Table 31 presents the sensitivity analyses of key parameters discussed above.

Table 31   One-way sensitivity analyses of key parameters, Population 1

Sensitivity analyses	MTA	RFA	Incremental cost per patient
Base case	**$7,235**	**$7,235**	**$0**
Weighted MBS fee for MTA: $962	$7,380	$7,235	$145
Reducing hospital costs of MTA by 10%	$6,611	$7,235	−$624
Reducing hospital costs of MTA by 20%	$5,988	$7,235	−$1,247
Reducing 1 basic units of anaesthesia for MTA	$7,215	$7,235	−$20
Reducing 2 basic unit of anaesthesia for MTA	$7,195	$7,235	−$40

Sensitivity analyses	MTA	RFA	Incremental cost per patient
Number of MTA sessions required per patient: 2.4	$17,364	$7,235	$10,129
Number of RFA sessions required per patient: 1.2	$7,235	$8,682	−$1,447

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cells show analyses indicating a potential cost saving (negative value for incremental cost) with the proposed treatment with MTA

As seen in Table 31, the MBS fee for MTA, hospital costs and the number of sessions required for either procedure are the key drivers of the economic analysis. If treatment with MTA results in a reduction in associated hospital costs or the number of sessions required compared with RFA, it may result in potential cost-savings when the same blanket fee as RFA is applied.

However, if the proposed graduated fee scheme is applied (see Appendix I for detailed multiway sensitivity analyses incorporating fee change and other factors), the incremental cost will vary in the range of −$814 to +$11,648 with a base-case incremental cost of $633 (see Table 76, Appendix I).

POPULATION 2

D.5.B RESULTS OF THE ECONOMIC EVALUATION

When only the procedural costs of MTA and RFA are compared (excluding all other associated anaesthetic and other healthcare costs), there is no incremental cost associated with MTA for the base case (Table 32).

Table 32   Incremental cost of MTA excluding other associated costs, Population 2

Item description	MTA	RFA	Incremental cost
Ablation procedure	$817	$817	$0

MTA = microwave tissue ablation; RFA = radiofrequency ablation

When all other associated healthcare costs are included in the analysis, the cost of both MTA and RFA is estimated to be $8,039. And since all other healthcare costs are considered to be similar across the two procedures, the incremental cost remains the same (that is, $0).

Table 33 shows the overall costs and the incremental cost per patient as calculated for the intervention and comparator in the analysis, with the base-case assumptions.

Table 33   Costs associated with MTA and RFA, Population 2

Item description	MTA	RFA
Ablation procedure	$817	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Chemotherapy	$805	$805
Other hospital costs	$6,236	$6,236
Total	**$8,039**	**$8,039**
Incremental cost per patient		**$0**

D.6.B SENSITIVITY ANALYSES

Sensitivity analyses are presented in Table 34, and include assessment of the cost impact of varying costs associated with procedures: MBS fees charged (stratified on the basis of number of lesions), hospital costs, anaesthesia cost and number of ablation sessions required. An additional analysis assumed a 10 per cent relative reduction in chemotherapy usage with MTA.

A sensitivity analysis considering the weighted cost of MTA based on the number of lesions treated per patient ($817 for treating up to 5 lesions, $1,300 for treating >5 lesions) was performed. Approximately 60 per cent of the patient population with liver cancer metastasis is estimated to have more than five lesions (see Table 72, Appendix I, for further details). The weighted cost of MTA based on a 40:60 per cent stratification equates to $1,107.

MBS data suggested that, on average, patients required 1.1–1.2 RFA sessions (see section D.4.4) for treating primary HCC. No such data are available to estimate the number of ablation sessions required per patient for Population 2 with secondary liver metastasis. This patient group is expected to be sicker and to have more liver lesions than Population 1. As such, the number of sessions required per patient may be higher than for Population 1.

Table 34   One-way sensitivity analyses of key parameters, Population 2

Sensitivity analyses	MTA	RFA	Incremental cost per patient
Base case	**$8,039**	**$8,039**	**$0**
Weighted MBS fee of MTA: $1,107	$8,329	$8,039	$290
Reducing hospital costs of MTA by 10%	$7,416	$8,039	−$624
Reducing hospital costs of MTA by 20%	$6,792	$8,039	−$1,247
Reducing 1 basic unit of anaesthesia for MTA	$8,019	$8,039	−$20
Reducing 2 basic units of anaesthesia for MTA	$8,000	$8,039	−$40
Number of MTA sessions required per patient: 2.4	$19,294	$8,039	$11,255
Number of RFA sessions required per patient: 1.2	$8,039	$9,647	−$1,608
Number of RFA sessions required per patient: 2	$8,039	$16,078	−$8,039
Relative reduction of 10% in chemotherapy usage with MTA	$7,887	$8,039	−$152

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cells show analyses indicating a potential cost saving (negative value for incremental cost) with the proposed treatment with MTA

As seen in Table 34, the MBS fee for MTA, hospital costs and the number of sessions required for either procedure are the key drivers of the economic analysis. If treatment with MTA results in a reduction in associated hospital costs or in the number of sessions compared with RFA, it may result in potential cost-savings when the same fee as RFA is applied.

However, if the proposed graduated fee scheme is applied (see Appendix I for detailed multiway sensitivity analyses; ie, incorporating fee change and other factors), the incremental cost will vary from −$7,077 to +$13,567 with a base-case incremental cost of $963 (see Table 79, Appendix I).

SECTION E   FINANCIAL IMPLICATIONS

E.1.   JUSTIFICATION OF THE SELECTION OF DATA SOURCES

MTA is proposed as an additional, potentially curative tumour ablation technique for patients with primary liver lesions or liver metastases from extrahepatic primary cancers, who are *not candidates for surgical resection*. To estimate the target patient population, an epidemiological approach was used. This is difficult to validate with a market-based estimate, as the existing comparator (RFA) is restricted to a narrower population than the proposed listing for MTA.[11]

For *Population 1* (patients with primary liver cancers), the estimated number of patients in Australia eligible for MTA is derived using the incidence of primary liver cancer identified by the Australian Institute of Health and Welfare (AIHW) (Australian Institute of Health and Welfare 2016b). PASC has advised that, if listed, MTA will entirely replace RFA in patients with HCC.

For *Population 2* (patients with secondary liver cancers), feedback suggested that ablative technologies are used primarily to treat CRC liver metastases, and are not routinely considered to treat other types of liver metastases (MSAC 2016). The incidence of CRC was also identified using AIHW data (Australian Institute of Health and Welfare 2016a), and the proportion with metastatic disease was based on rates reported in the literature. These were used as the basis for the estimate of potential patient usage.

In *Population 3* (patients with unresectable neuroendocrine liver metastases with or without extrahepatic spread who are refractory to somatostatin analogue therapy), MTA is proposed to be used for palliative treatment of secretory syndromes. Feedback suggested that tumour ablation in this population would rarely be used, as these patients are managed primarily by chemotherapy. No further data were available on this potential population. Therefore, the expected number of ablations that would be performed in Population 3 could not be included in this analysis.

For Populations 1 and 2, the percentages of patients with liver cancers *that are unresectable but are ablatable* (ie, as required for eligibility) are estimated on the basis of the proportions of patients treated with ablation, in each population, identified in the literature. However, this eligibility criterion is not easily defined and is potentially subjective, and therefore the estimates are uncertain.

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[11] RFA is not MBS-listed for the ablation of other liver primaries or secondary liver cancers. Available hospital data on the number of ablations performed annually does not distinguish between RFA and MTA procedures, nor whether they were undertaken for patients with HCC, non-HCC liver cancers or secondary metastases. As such, the data cannot be used to inform a market-based prediction of the number of likely MTA services.

The data sources used to calculate the financial impact of the MBS listing of liver MTA are summarised in Table 35.

Table 35   Parameters and data sources used in the financial analysis

Data source	Purpose	Value
Epidemiological data		
ACIM books (Australian Institute of Health and Welfare 2016a, 2016b)	Estimate of incidence of *primary* liver cancer and CRC in Australia (per 100,000)	Estimated for 2017: Liver: 7.2 CRC: 62.0 (as per calculations in E.1.1)
Colorectal liver metastases: (Neo et al 2011)	Estimate of incidence of colorectal liver metastases	15%–25%
ABS data catalogue no. 3222, series B (Australian Bureau of Statistics 2013)	Projection of Australian population, all ages in 2017–2022	Row A, Table 36
Market data		
(MSAC 2003)	Proportion of primary liver cancer patients treated with ablation	25%
Expert advice (MSAC 2003; Neo et al 2011)	Proportion of secondary liver cancer patients treated with ablation	Base case: 5% Sensitivity analysis: 1% and 10%
AIHW procedure data cubes (AIHW National Hospital Morbidity Database 2015)	Number of ablation procedures performed annually in 2011–12 to 2013–14	Table 81, Appendix I
MBS data for current RFA services (MBS items 50950 and 50952)	Average MBS benefit paid per service, 2014–15	MBS item 50950: $659 MBS item 50952 : $592
-	Estimated average bulk-billing rate	MBS item 50950: 40% MBS item 50952 : 0%
-	Average co-payment per service (private sector, patient or insurer)	MBS item 50950: $94 MBS item 50952 : $512
-	Split between percutaneous and laparoscopic/surgical RFA	93% and 7%
Expert advice	Stratification of patients based on number of lesions per patient—up to 3 lesions, 4–5 lesions and >5 lesions (analyses presented in Appendix K)	Population 1: 70%, 15%, 15% Population 2: 60%, 20%, 20%
MTA MBS fee	Cost of MTA to the MBS and private sector co-payments	Base case: $817.10
MBS data for item 50950	Proportion of services in private hospital inpatient setting for Population 1	60%
(AIHW National Hospital Morbidity Database 2015) and MBS data for items 50950 and 50952 for years 2011–2014	Proportion of ablation services performed in private and public sectors	27%

ABS = Australian Bureau of Statistics; ACIM = Australian Cancer Incidence and Mortality; AIHW = Australian Institute of Health and Welfare; CRC = colorectal cancer; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; MTA = microwave tissue ablation; RFA = radiofrequency ablation

The usage and financial estimates in this report are presented for the five financial years, 2017–18 to 2021–22. *To aid interpretation, tables used for epidemiological calculations are allocated consistent row identifiers that continue consecutively throughout the sections.*

For each year of analysis, the following steps are taken to estimate the number of patients with primary or secondary liver tumours for whom it would be appropriate to use MTA:

1. Identify the **projected Australian population**. Estimate Australian **incidence rates of (i) liver cancer** (ie, all primary liver cancer, including HCC, cholangiosarcoma, angiosarcoma and hepatoblastoma), using the observed trend in the incidence of liver cancer over time, and **(ii) colorectal cancer** (CRC).

2. Using the values identified in step 1, estimate the incident number of patients with **primary liver cancer**, and within that population, estimate the number **eligible for ablation** (based on estimated rate of patients with HCC suitable for RFA).

3. Using the values identified in step 1, estimate the incident number of patients with **CRC** and identify the proportion and number with **colorectal liver metastases** (CRLM) at the time of diagnosis, and within that population, estimate the number **eligible for ablation** (based on estimated rate of patients with CRLM suitable for RFA).

POPULATION 1

E.2.A   USE AND COSTS OF MTA

E.2.A.1   PROJECTED AUSTRALIAN POPULATION AND INCIDENCE RATES OF PRIMARY LIVER CANCER

For each year, the total projected Australian population is the sum of the projected population for each age, as estimated by the Australian Bureau of Statistics (Australian Bureau of Statistics 2013). This estimate is presented in Row A, Table 36.

The incidence of liver cancer in Australia was extracted from the *Australian Cancer Incidence and Mortality* books for liver (Australian Institute of Health and Welfare 2016b). Data show that the incidence of primary liver cancer has steadily increased over the past 29 years, with the Australian age-standardised incidence rising from 1.8 per 100,000 in 1982 to 6.4 per 100,000 in 2012 (Figure 8, Appendix J).

The available data for the period 1982–2012 were projected over the next 10 years (2013–2022) assuming a linear increase in the rate of liver cancer (Figure 8, Appendix J). Table 80 (Appendix J) shows the estimated incidence of liver cancer in Australia, calculated on the basis of the linear increase demonstrated in Figure 8, including the estimated incidence rates for 2017–2022 which are used in this report.

E.2.A.2   ESTIMATED NUMBER OF PATIENTS WITH PRIMARY LIVER CANCER ELIGIBLE FOR MTA

Table 36 presents the projected incident rates and number of cases for primary liver cancer for the years 2017–2022. Although approximately 70 per cent of patients with primary liver cancer have

unresectable tumours, not all of them are eligible for liver ablation. The applicant's advice to MSAC application 1052 (RFA of liver tumours) suggested that nearly 25 per cent of patients with HCC may be eligible for liver ablation (MSAC 2003), although this estimate could not be confirmed it is used in the base-case calculations.

Table 36   Projected incident cases of primary liver cancer eligible for MTA, Population 1

Row		2017–18	2018–19	2019–20	2020–21	2021–22
A	Projected number of Australians, all ages (Australian Bureau of Statistics 2013)	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
B	Estimated incident rate of primary liver cancer per 100,000 (Table 80, App I)	7.2	7.4	7.6	7.8	7.9
C	Number of incident cases of primary liver cancer (= A × B)	1,796	1,870	1,946	2,022	2,100
D	**Number of patients with primary liver cancer eligible for MTA (= C × 25%)**	**449**	**468**	**486**	**506**	**525**

MTA = microwave tissue ablation

Source: Eligibility for ablation rate (25%) sourced from (MSAC 2003)

E.2.A.3   ELIGIBLE PATIENTS AND UPTAKE RATE WITH MBS SUBSIDISATION

The applicant has suggested that MTA (and RFA) is currently performed both percutaneously and laparoscopically in both public and private hospitals within Australia, despite there being no MBS subsidisation of MTA in the private sector. Data on liver ablation procedures undertaken currently in Australian hospitals are presented in Table 81, Appendix J; in 2013–14, a total 418 liver ablation procedures were undertaken in Australian hospitals (311 specifically RFA). The projected estimates in Table 36 project slightly higher rates of liver ablation than currently occurs. This is consistent with a broadening of the indication (compared with the current listing of RFA) and an anticipated increase in the accessibility of MTA in the private sector associated with an MBS listing.

Currently, the proportion of RFAs obtaining Medicare funding can be determined by dividing the total number of RFAs (Table 81, Appendix J) by the number of services for MBS items 50950 and 50952 in the same year. Between 26 and 29 per cent of liver RFAs were MBS funded in 2011–2014 (Table 37).

Table 37   Proportion of RFAs obtaining MBS subsidy

Row	MBS item	2011–12	2012–13	2013–14	2014–15	2015–16
E	50950 RFA (percutaneous)	91	78	86	96	119
F	50952 RFA (open or laparoscopic)	2	6	4	15	17
G	**Total MBS-funded RFAs**	**93**	**84**	**90**	**111**	**136**
H	All RFAs performed [a]	359	325	311	NA	NA
I	**% of RFAs with MBS subsidy (= G/H)**	**26%**	**26%**	**29%**	**NA**	NA

[a] Data presented in Table 81, Appendix J

MBS = Medicare Benefits Schedule; NA = not available; RFA = radiofrequency ablation

Feedback suggested that MTA is expected to fully replace RFA and, that if Medicare funding were approved, there may be an increase in MTA services undertaken in the private sector. It is assumed that if Medicare funding for MTA were approved, there would initially be a similar proportion of MBS-funded services, and then increasing private sector use over time. Therefore, a gradual extension of use of MTA services in the private sector (from 29 to 37 per cent) is included in the financial analysis presented in Table 38 (and varied in sensitivity analyses in Section E.6.a).

In addition, the proportion of RFAs performed percutaneously in private hospitals is derived from Table 37 (the number of services of item 50950, row E, divided by the total number of RFA services performed, row G). On average, within private hospitals, 93 per cent of RFAs are performed percutaneously.[12]

Table 38 summarises the expected number of MTA services, and the split between percutaneous and laparoscopic/open surgery MTAs in private hospitals, over the first 5 years of listing.

Table 38   Estimate of MTA services that would be performed in private hospitals

Row		2017–18	2018–19	2019–20	2020–21	2021–22
J	Total number of eligible MTA services (row D, Table 36)	449	468	486	506	525
K	Estimated proportion of RFAs performed in private hospitals[1]	29%	31%	33%	35%	37%
L	**Estimated number of MBS-funded MTA services**	**130**	**145**	**160**	**176**	**194**
M	Number of percutaneous MTAs	121	135	149	164	180
N	Number of intraoperative MTAs	8	9	10	11	13

[1] Assuming 2% increase every year. Baseline average proportion is assumed as 27% (average of values in Row I, Table 37)

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

E.2.A.4   ESTIMATED COST OF MTA TO THE MBS

It is assumed that if MTA were MBS listed, patterns for MBS subsidy, bulk-billing and co-payments would be similar to those that occur with RFA. Data on the average of fees charged, benefits paid, patient co-payments and bulk-billing rates per service for MBS items 50950 and 50952 were provided by the Australian Government Department of Health and are summarised in Table 39. The data suggest that all outpatient services are bulk-billed, as there are no average patient co-payments for outpatient services for RFA (co-payments for all inpatient services; 25 per cent of the scheduled fee; may be contributed by insurer or patient).

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[12] Proportions of RFAs performed percutaneously, derived from row E ÷ row G in Table 37: 2011–12, 98%; 2012–13, 93%; 2013–14, 96%; 2014–15, 86%; 2015–16, 88%.

Table 39   MBS data and cost of RFA in the year 2014–15

Row	Description	Percutaneous RFA (MBS item 50950)	Intraoperative RFA (MBS item 50952)
O	Proportion of services performed as outpatient	40%	0%
P	Scheduled fee	$817	$817
Q	Average fee charged per service	$816	$1,104
R	Average benefit paid (cost to MBS)	$659	$592
S	Bulk billing rate	40%	0%
T	Average patient contribution per outpatient service	$0	$0
U	Average co-payment per service [= (Q – R) × (1 – S)]	$94	$512
V	**Total cost of RFA (including co-payment) (= R + U)**	**$754**	**$1,104**

MBS = Medicare Benefits Schedule; RFA = radiofrequency ablation

Applying a similar pattern to MTA services, it is assumed that 40 per cent of percutaneous MTA services would be outpatient services and all bulk-billed. The cost to MBS is 75 per cent of the proposed fee for inpatient services and 85 per cent for outpatient services. Co-payments for the inpatient services are calculated as 25 per cent of the proposed fee. Table 40 summarises all the steps taken to estimate the weighted average cost of MTA (to MBS and co-payment) per service.

The base-case calculations assume the cost of MTA to be the same as RFA; additional financial analyses using the proposed stratified fee for MTA are presented in Appendix K. Table 40 lists estimated costs of MTA for both percutaneous and laparoscopic procedures, incorporating the bulk-billing and outpatient services pattern.

Table 40   Estimated cost of per MTA procedure

Row	Description	Percutaneous MTA	Intraoperative MTA
W	MBS fee	$817	$817
X	Average cost to MBS [1]	$646	$613
Y	Average co-payment per service [1]	$123	$204

[1] Calculated as weighted average of fee/benefit paid for inpatient (60%) and outpatient services (40%)

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 41 provides the estimated cost of MTA services to MBS.

Table 41   Estimated cost of MTA services to MBS

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
M	Number of percutaneous services	121	134	149	164	180
Z	Total MBS cost of percutaneous MTA at $646/service (= X × M)	$77,894	$87,008	$96,054	$105,913	$116,301
N	Number of intraoperative services	8	9	10	11	13
AA	Total cost MBS cost of intraoperative MTA at $613/service (= X × N)	$5,176	$5,763	$6,383	$7,039	$7,729
AB	**Total cost of MTA to MBS (= Z + AA)**	**$83,070**	**$92,482**	**$102,437**	**$112,952**	**$124,030**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 42 summarises estimated costs of MTA services incurred by the private sector.

Table 42   Estimated cost of MTA services to private sector (co-payments)

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
M	Number of percutaneous services	121	134	149	164	180
AC	Total co-payments of percutaneous MTA (= Y × M)	$14,790	$16,466	$18,238	$20,110	$22,083
N	Number of intraoperative services	8	9	10	11	13
AD	Total co-payments for intraoperative MTAs (= Y × N)	$1,725	$1,921	$2,128	$2,346	$2,576
AE	**Total cost of MTA to private sector**	**$16,515**	**$18,387**	**$20,366**	**$22,456**	**$24,659**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.3.A   CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

E.3.A.1   ESTIMATED SERVICES OFFSET

Both RFA and MTA are being performed in public and private hospitals. Currently RFA in Population 1 is restricted to primary HCC. If listed, MTA would fully replace RFA. MTA listing may result in a small growth in the market for liver tumour ablations (due to broadening of the listing to include all primary liver cancers), primarily through an extension of services in the private sector, resulting in cost shifts from state government healthcare budgets to the MBS. It is assumed that in the absence of MTA listing, linear growth of RFA ablation would continue, of which 27 per cent would be performed with MBS subsidy in private hospitals (Table 43).

Table 43   Estimation of the number of comparator services offset

Row		2017–18	2018–19	2019–20	2020–21	2021–22
J	Number of eligible MTA services	449	468	486	506	525
AF	**Total number of tests offset (= 27% × J)**	**121**	**126**	**131**	**137**	**142**
AG	Number of percutaneous RFAs (= 93% × AF)	113	117	122	127	132
AH	Number of intraoperative RFAs (= 7% × AF)	8	9	9	10	10

MTA = microwave tissue ablation; RFA = radiofrequency ablation

E.3.A.2   ESTIMATED COSTS OFFSET

The estimated costs per service to the MBS and to the private sector used in the financial model are presented in Table 39, and are based on the average MBS benefit and co-payments paid per service in 2014–15 for each of the RFA services.

RFA performed in public hospitals has no associated MBS services, and the costs of the procedure are incurred by state healthcare budgets. In contrast, RFA performed in private hospitals has charges associated with Medicare services and hospital components, and the costs are incurred by Medicare, patients and private health insurers (PHIs). Only costs associated with procedures done in private settings are considered in the financial analysis. Table 44 presents the estimated total costs offset by comparator services.

Table 44   Total costs offset by RFA services

	2017–18	2018–19	2019–20	2020–21	2021–22
Number of services offset					
Percutaneous RFAs	113	117	122	127	132
Intraoperative RFAs	8	9	9	10	10
MBS costs offset					
Percutaneous RFAs	$74,348	$77,413	$80,534	$83,711	$86,939
Intraoperative RFAs	$5,028	$5,235	$5,446	$5,661	$5,879
Total offsets to MBS	**$79,376**	**$82,648**	**$85,980**	**$89,371**	**$92,818**
Co-payment costs offset					
Percutaneous RFAs	$10,615	$11,053	$11,498	$11,952	$12,412
Intraoperative RFAs	$4,345	$4,524	$4,706	$4,892	$5,081
Total offsets to co-payments	**$14,960**	**$15,576**	**$16,204**	**$16,844**	**$17,493**
Total costs offset	**$94,335**	**$98,225**	**$102,184**	**$106,215**	**$110,311**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

E.4.A   FINANCIAL IMPLICATIONS FOR THE MBS

Table 45 summarises the financial implications to the MBS over the next 5 years resulting from the proposed listing of MTA.

Table 45   Total costs to the MBS associated with MTA

-	2017–18	2018–19	2019–20	2020–21	2021–22
MTA					
Number of MBS services	130	144	160	176	194
Cost to the MBS	$83,070	$92,482	$102,437	$112,952	$124,030
MBS services offset					
Number of MBS services offset	121	126	131	137	142
Costs offset	$79,376	$82,648	$85,980	$89,371	$92,818
Net cost to the MBS	**$3,695**	**$9,833**	**$16,457**	**$23,580**	**$31,212**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.5.A   FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

There may be some financial implications (cost-savings) for state and territory government health budgets, such as for public hospitals (including inpatient admissions, emergency department visits and outpatient clinic visits) due to the extension of services in the private sector. However, quantification of such cost shifts (from state health budgets to MBS) is harder, since the proposed listing is much broader than the existing listing for RFA, and because both RFA and MTA are being performed currently in Australian hospitals.

Table 46 presents the estimated financial implications of the proposed MTA listing (assuming no growth in the market) for other healthcare budgets. These estimates should be interpreted with caution as there may be some increase in the number of ablations performed in clinical practice, in which case the estimates presented will overestimate the cost offsets associated with MTA listing. The cost of ablation services performed in public hospitals is taken from AR-DRG H05B (Hepatobiliary Diagnostic Procedures without Catastrophic Complications) (Independent Hospital Pricing Authority (IHPA) 2015a) and adjusted for inflation: $6,840 ($7,048 in 2016 AUD)[10]. MTA performed in the private sector will incur costs to Medicare, private hospitals and patients or PHIs. Costs to PHIs are calculated as the sum of healthcare costs excluding costs to Medicare (see Table 28, Section D.4.5) and co-payments associated with MTA ($6,236 + $204 = $6,440).

Table 46   Cost implications for other healthcare budgets (assuming no growth in number of ablations)*

-	2017–18	2018–19	2019–20	2020–21	2021–22
State governments: number of MTA services offset	9	19	29	40	52
Cost savings to state governments	$58,258	$127,921	$196,182	$273,085	$355,445

* It is assumed that there would be no growth in the number of ablations performed; and there will be extension of services in the private settings. Thus, a cost shift from public sector to private sector.
MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 47 presents the financial implications to the private sector (patients or PHI) of listing MTA.

Table 47   Total costs to private sector associated with MTA listing for Population 1

-	2017–18	2018–19	2019–20	2020–21	2021–22
Number of MTA services	130	145	160	176	194
Cost to private sector	$825,654	$922,268	$1,018,149	$1,122,653	$1,232,765
Offsets					
Number of services offset	121	126	131	137	142
Costs offset	$770,986	$802,774	$835,134	$868,077	$901,550
Net costs to private sector (including co-payments)	$54,668	$119,493	$183,015	$254,576	$331,215

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

As seen in Table 46 and Table 47, MTA listing may result in cost shifting from the state government healthcare budgets to Medicare and PHI.

E.6.A   IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Table 48 presents sensitivity analyses around inputs to the financial model.

Table 48   Sensitivity analysis of financial implications of listing MTA for Population 1

-	2017–18	2018–19	2019–20	2020–21	2021–22
Base case					
Net cost of MTA to the MBS	**$3,695**	**$10,142**	**$16,457**	**$23,580**	**$31,212**
Net cost of MTA to the private sector[1]	**$1,556**	**$2,872**	**$4,162**	**$5,613**	**$7,166**
Proportion of patients eligible for ablation: 20% (base case: 25%)					
Net cost of MTA to the MBS	$2,956	$8,114	$13,166	$18,864	$24,970
Net cost of MTA to the private sector	$1,245	$2,297	$3,329	$4,490	$5,733
Weighted MBS fee for MTA: $962 (base case $817.10)					
Net cost of MTA to the MBS	$18,426	$26,597	$34,623	$43,610	$53,207
Net cost of MTA to the private sector	$4,485	$6,143	$7,773	$9,595	$11,539
Assuming no extension of services in private sector (base case 2%–10%)					
Net cost of MTA to the MBS	−$1,758	−$1,831	−$1,904	−$1,980	−$2,056
Net cost of MTA to the private sector	$472	$491	$511	$531	$552
Assuming all services as inpatient (base case: 60%)					
Net cost of MTA to the MBS	−$249	$5,443	$11,594	$18,217	$25,324
Net cost of MTA to the private sector	$11,416	$13,787	$16,320	$19,019	$21,887
Assuming 80% services as inpatient (base case: 60%)					
Net cost of MTA to the MBS	$1,723	$7,638	$14,026	$20,899	$28,268
Net cost of MTA to the private sector	$6,486	$8,299	$10,241	$12,316	$14,527

[1] Net costs to private sector in this table represent co-payments only and exclude all other hospital costs.

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

POPULATION 2

E.2.B   USE AND COSTS OF MTA

E.2.B.1   INCIDENCE RATES OF COLORECTAL CANCER

The incidence of CRC in Australia was extracted from the *Australian Cancer Incidence and Mortality* books for bowel cancer (Australian Institute of Health and Welfare 2016a).

The trend in the incidence of CRC is unpredictable. The age-standardised incidence rate has varied inconsistently between 58 and 66 per 100,000 (Figure 8, Appendix J). For this report, a constant incidence rate of 62 per 100,000 (the average for 1982–2012) is assumed.

E.2.B.2   ESTIMATED NUMBER OF PATIENTS WITH SECONDARY LIVER METASTASES ELIGIBLE FOR MTA

Table 49 presents the projected incident rate (row B), the projected number of cases of CRC (row C) and the estimated number of cases with colorectal liver metastases (CRLM) (row D) for 2017–2022.

The MSAC protocol for liver MTA suggests that approximately 20–25 per cent of incident cases of CRC will present with liver metastases at the time of diagnosis (MSAC 2016). The lower value is used to derive the incident case of CRLM in base-case analysis, and the upper value is assessed in the sensitivity analysis.

The applicant's advice to MSAC application 1052 (RFA of liver tumours) suggested that 10 per cent of patients with CRLM are suitable for ablative therapies (MSAC 2003). However, this estimate varies from the expert advice to the current assessment that approximately 5 per cent of patients with liver metastases are suitable. The base-case analysis assumes a 5 per cent ablation rate in Population 2, whereas the sensitivity analyses use 1 and 10 per cent.

Table 49   Projected incident cases of colorectal liver metastases eligible for MTA, Population 2

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
A	Projected number of Australians, all ages (Australian Bureau of Statistics 2013)	24,781,121	25,201,317	25,619,895	26,037,356	26,452,147
B	Rate of CRC incidence per 100,000 (Table 80, Appendix I)	62	62	62	62	62
C	Number of incident cases of CRC (= A × E)	15,364	15,625	15,884	16,143	16,400
D	Number of incident cases of metastatic colorectal liver cancer (= F × 20%)	3,073	3,125	3,177	3,229	3,280
E	**Number of eligible MTA services in patients with colorectal liver metastases (= G × 5%)**	154	156	159	161	164

CRC = colorectal cancer; MTA = microwave tissue ablation

Source: Eligibility for ablation—5% of the incident cases of metastatic colorectal liver cancer, clinical expert advice[6]

Currently, there is no Medicare funding available for RFAs performed in patients with secondary liver metastases. Approximately 27 per cent of the RFA services are performed in private hospitals for Population 1 (see Section E.2.a.3). It is assumed in the analysis that if Medicare funding for MTA were approved for Population 2, there will be a similar proportion of MBS-funded services as in Population 1 (from 29 to 37 per cent). Sensitivity analysis varying this assumption is presented in Section E.6.b.

Table 50 summarises the expected number of MTA services, in private hospitals, over the first 5 years of listing.

Table 50   Estimate of MTA services that would be performed in private hospitals

Row	-	2017–18	2018–19	2019–20	2020–21	2021–22
E	Total number of eligible MTA services	154	156	159	161	164
F	Estimated proportion of MTAs performed in private hospitals[1]	29%	31%	33%	35%	37%
G	**Estimated number of MBS-funded MTA services**	**45**	**48**	**52**	**57**	**61**

[1] Assuming 2% increase every year. Baseline average proportion is assumed as 27% (see Row I, Table 37)

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.2.B.3   ESTIMATED COST OF MTA TO THE MBS

It is assumed that all MTAs and RFAs in Population 2 are performed as inpatient services, so the benefits paid and co-payments (25 per cent of the MBS fees) would be similar across percutaneous and laparoscopic/open procedures. Henceforth, costs of MTA are not segregated by procedure.

The base case uses the MBS fee for RFA for MTA also (Table 51). Appendix K presents economic analyses comparing costs of MTA and RFA based on the proposed stratified fees.

Table 51   Cost of MTA and RFA

Row	Description	RFA	MTA
H	MBS fee	Not listed	$817
I	Benefit paid (= 75% × H)	–	$613
J	Co-payment per service (= 25% × H)	–	$204
K	**Total cost per procedure (including co-payment)**	**–**	**$817**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Table 52 provides the estimated costs of MTA services to MBS over the first 5 years of listing.

Table 52   Estimated cost of MTA services to MBS and private sector (co-payments)

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
G	Estimated number of MBS-funded MTA services	45	48	52	57	61
L	**Total cost of MTA to MBS (= I × G)**	**$27,305**	**$29,683**	**$32,123**	**$34,625**	**$37,187**
M	**Total cost of MTA to private sector (= J × G)**	**$9,102**	**$9,894**	**$10,708**	**$11,542**	**$12,396**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.3.B   CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

E.3.B.1   ESTIMATED SERVICES OFFSET

Currently RFA is not MBS listed for Population 2; thus, there are no cost offsets in the private sector. However, both MTA and RFAs are performed in public and private hospitals for patients with unresectable secondary liver metastases. If listed, MTA may result in the extension of services in the private sector, therefore resulting in cost shifts from state government health budgets to the MBS. It

is assumed that in the absence of MTA listing, none (0 per cent) of the ablations would be performed with an MBS subsidy in private hospitals (Table 53).

Table 53   Estimation of the number of comparator services offset

Row	-	2017–18	2018–19	2019–20	2020–21	2021–22
E	Number of eligible MTA services	154	156	159	161	164
N	Total number of RFA services offset (= 0% × E)	0	0	0	0	0

MTA = microwave tissue ablation; RFA = radiofrequency ablation

E.3.B.2   ESTIMATED COSTS OFFSET

The estimated costs per service to the MBS and to the private sector used in the financial model are presented in Table 51. RFAs performed in public hospitals have no associated MBS services, and the costs of the procedure are incurred by state healthcare budgets. Since RFA is not listed for Population 2, RFAs performed in private hospitals have the costs incurred by patients and PHIs.

The financial analysis considers only costs associated with procedures done in private settings. As there are no data available to estimate the number of RFA services currently performed in private settings for Population 2, it is considered that all services are performed in public hospitals. Thus, there are no MBS costs or co-payments associated with comparator services (Table 54).

Table 54   Total costs offset by MTA services

-	2017–18	2018–19	2019–20	2020–21	2021–22
Number of services offset	0	0	0	0	0
Costs offset to the MBS	$0	$0	$0	$0	$0
Costs offset to co-payments	$0	$0	$0	$0	$0
Total costs offset	**$0**	**$0**	**$0**	**$0**	**$0**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.4.B   FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of MTA over the next 5 years are summarised in Table 55.

Table 55   Total costs to the MBS associated with MTA

-	2017–18	2018–19	2019–20	2020–21	2021–22
MTA					
Number of MBS services	45	48	52	57	61
Cost to the MBS	$27,305	$29,683	$32,123	$34,625	$37,187
MBS services offset					
Number of MBS services offset	0	0	0	0	0
Costs offset	$0	$0	$0	$0	$0
Net cost to the MBS	**$27,305**	**$29,683**	**$32,123**	**$34,625**	**$37,187**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.5.ʙ Financial Implications for Government Health Budgets

There may be some financial implications (cost-savings) for state and territory Government healthcare budgets, such as for public hospitals (including inpatient admissions, emergency department visits and outpatient clinic visits) due to the extension of services in the private sector. However, quantification of such cost shifts (from state government healthcare budgets to the MBS) is harder since there is no existing listing of RFA for Population 2, and because both RFA and MTA are being performed currently in Australian hospitals.

Table 56 presents the estimated financial implications of the proposed MTA listing (assuming that all ablations are currently performed in public hospitals) for other healthcare budgets. These estimates should be interpreted with caution as there may be some increase in the number of ablations performed in clinical practice, in which case the estimates will overestimate the cost offsets associated with MTA listing. The cost of ablation services performed in public hospitals is taken from the AR-DRG H05B (Hepatobiliary Diagnostic Procedures without Catastrophic Complications) (Independent Hospital Pricing Authority (IHPA) 2015a) and adjusted for inflation: $6,840 ($7,048 in 2016 AUD)[10]. MTA performed in the private sector will incur costs to Medicare, private hospitals and patients or PHI. Costs to PHIs are calculated as the sum of healthcare costs excluding costs to Medicare (Table 28, Section D.4.5) and co-payments associated with MTA ($6,236 + $204 = $6,440).

Table 56   Cost implications for other healthcare budgets (assuming no growth in number of ablations)*

-	2017–18	2018–19	2019–20	2020–21	2021–22
State governments: number of MTA services offset	45	48	52	57	61
Cost savings to state governments	$314,028	$341,377	$369,437	$398,212	$427,673

* It is assumed that there would be no growth in the number of ablations performed. and there will be extension of services in the private setting; thus, a cost shift from public sector to private sector
MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 57 presents the financial implications to the private sector (patients/PHI) of listing MTA.

Table 57   Total costs to private sector associated with MTA listing for Population 2

-	2017–18	2018–19	2019–20	2020–21	2021–22
Number of MTA services	45	48	52	57	61
Number of services offset	0	0	0	0	0
Net costs to private sector (including co-payments)	$286,956	$311,947	$337,588	$363,882	$390,804

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

E.6.ʙ Identification, Estimation and Reduction of Uncertainty

Table 58 presents sensitivity analyses around inputs to the financial model. The results show that the number of MTA services that would be performed affects the net cost of MTA to the MBS.

Table 58   Sensitivity analysis of financial implications of listing MTA for Population 2

-	2017–18	2018–19	2019–20	2020–21	2021–22
Base case					
Net cost of MTA to the MBS	**$27,305**	**$29,683**	**$32,123**	**$34,625**	**$37,187**
Net cost of MTA to the private sector[1]	**$9,102**	**$9,894**	**$10,708**	**$11,542**	**$12,396**
Proportion of patients eligible for ablation: 1% (base case: 5%)					
Net cost of MTA to the MBS	$5,461	$5,937	$6,425	$6,925	$7,437
Net cost of MTA to the private sector	$1,820	$1,979	$2,142	$2,308	$2,479
Proportion of patients eligible for ablation: 10% (base case: 5%)					
Net cost of MTA to the MBS	$54,611	$59,367	$64,246	$69,251	$74,374
Net cost of MTA to the private sector	$18,204	$19,789	$21,415	$23,084	$24,791
Proportion of CRM patients with CRLM: 25% (base case 20%)					
Net cost of MTA to the MBS	$34,132	$37,104	$40,154	$43,282	$46,484
Net cost of MTA to the private sector	$11,377	$12,368	$13,385	$14,427	$15,495
Weighted MBS fee for MTA: $1,107 (base case $817)					
Net cost of MTA to the MBS	$36,988	$40,209	$43,514	$46,903	$50,373
Net cost of MTA to the private sector	$12,329	$13,403	$14,505	$15,634	$16,791
Assuming 10% of services in private sector (base case 29%–37%)					
Net cost of MTA to the MBS	$9,416	$9,575	$9,734	$9,893	$10,051
Net cost of MTA to the private sector	$3,139	$3,192	$3,245	$3,298	$3,350
Assuming 20% of services in private sector (base case 29%–37%)					
Net cost of MTA to the MBS	$18,831	$19,151	$19,469	$19,786	$20,101
Net cost of MTA to the private sector	$6,277	$6,384	$6,490	$6,595	$6,700
Assuming 30% of services in private sector (base case 29%–37%)					
Net cost of MTA to the MBS	$28,247	$28,726	$29,203	$29,679	$30,152
Net cost of MTA to the private sector	$9,416	$9,575	$9,734	$9,893	$10,051

[1] Net cost to private sector in this table represents co-payments only and exclude all other hospital costs.

CRC = colorectal cancer; CRLM = colorectal liver metastases; MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

SECTION F   OTHER RELEVANT CONSIDERATIONS

Current clinical guidelines for the treatment of liver lesions were considered, but there were no references to MTA relevant to this assessment.

APPENDIX A   CLINICAL EXPERTS AND ASSESSMENT TEAM

CLINICAL EXPERT

Name	Expertise
Mr Brett KNOWLES	General and hepatobiliary surgeon
Dr Colin TAN	Interventional radiologist
Dr Chris ROGAN	Interventional radiologist

ASSESSMENT GROUP

Adelaide Health Technology Assessment

Name	Position
Joanne Milverton	Research officer
Jacqueline Parsons	Team Leader—Special projects
Ruchi Mittal	Health economist
Skye Newton	Team leader—Healthcare evaluation
Camille Schubert	Team Leader—Health economics

NOTED CONFLICTS OF INTEREST

There were no conflicts of interest.

APPENDIX B   CLINICAL MANAGEMENT ALGORITHMS
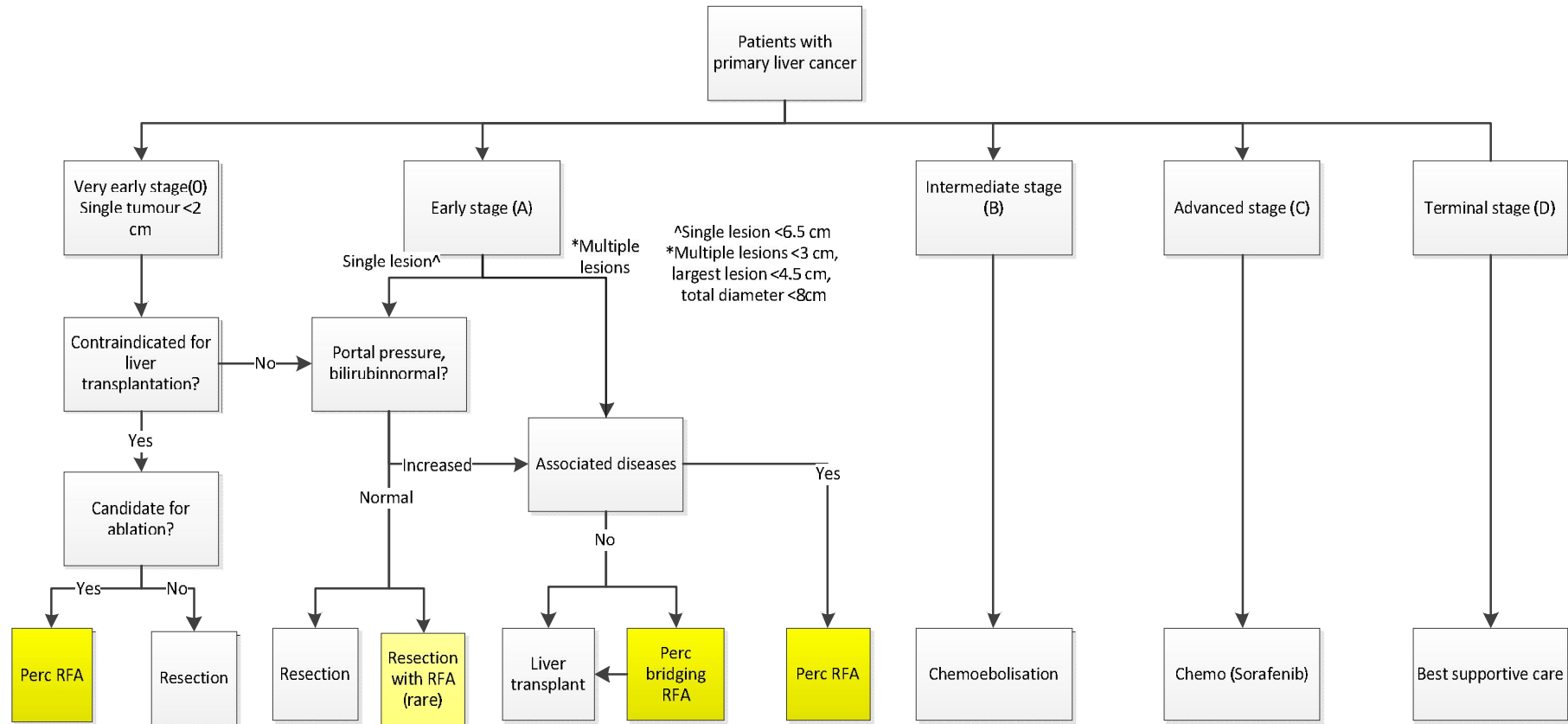
Figure 2   Current clinical practice for patients with primary unresectable liver lesions (Population 1)

RFA = radiofrequency ablation
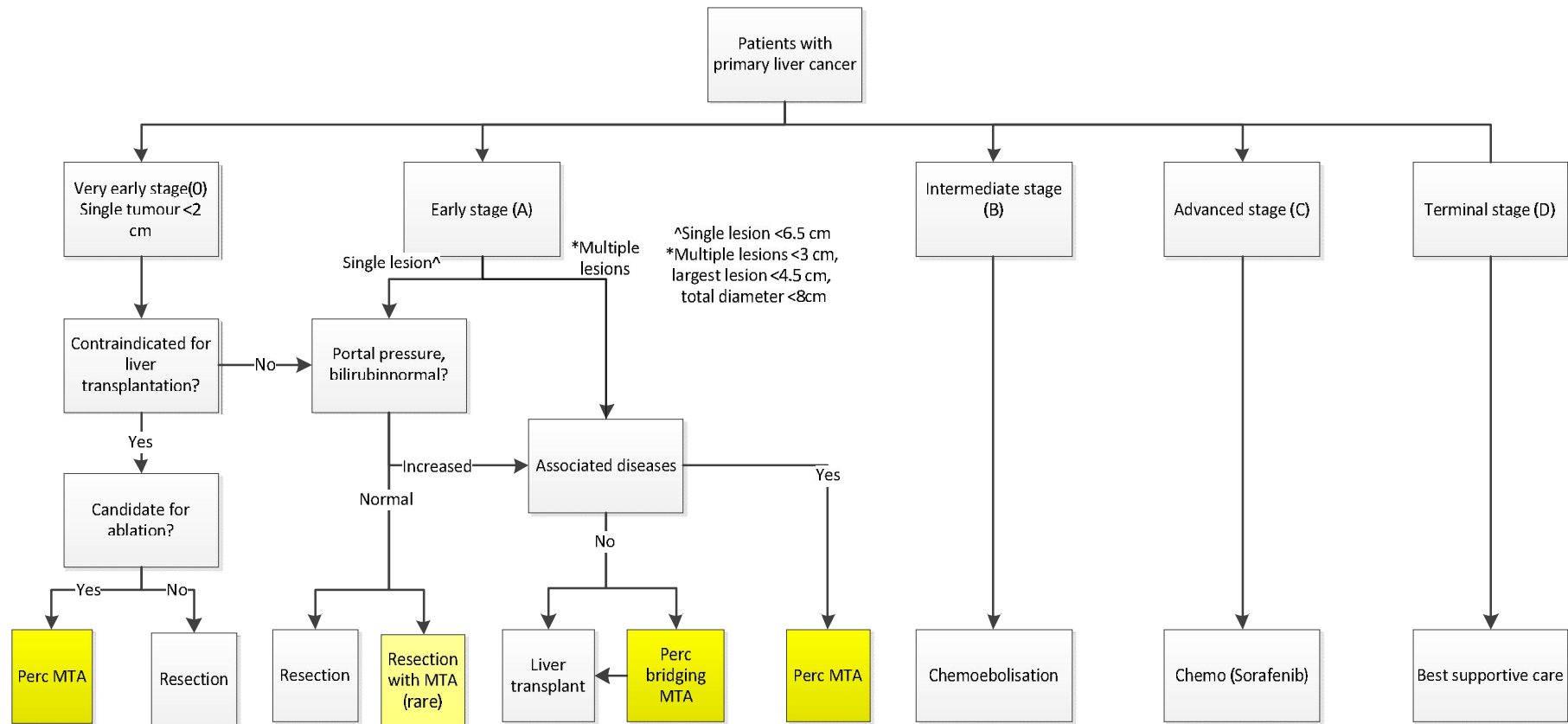
Figure 3   Proposed clinical practice for patients with primary unresectable liver lesions (Population 1)

Chemo = chemotherapy; MTA = microwave tissue ablation; perc = percutaneous
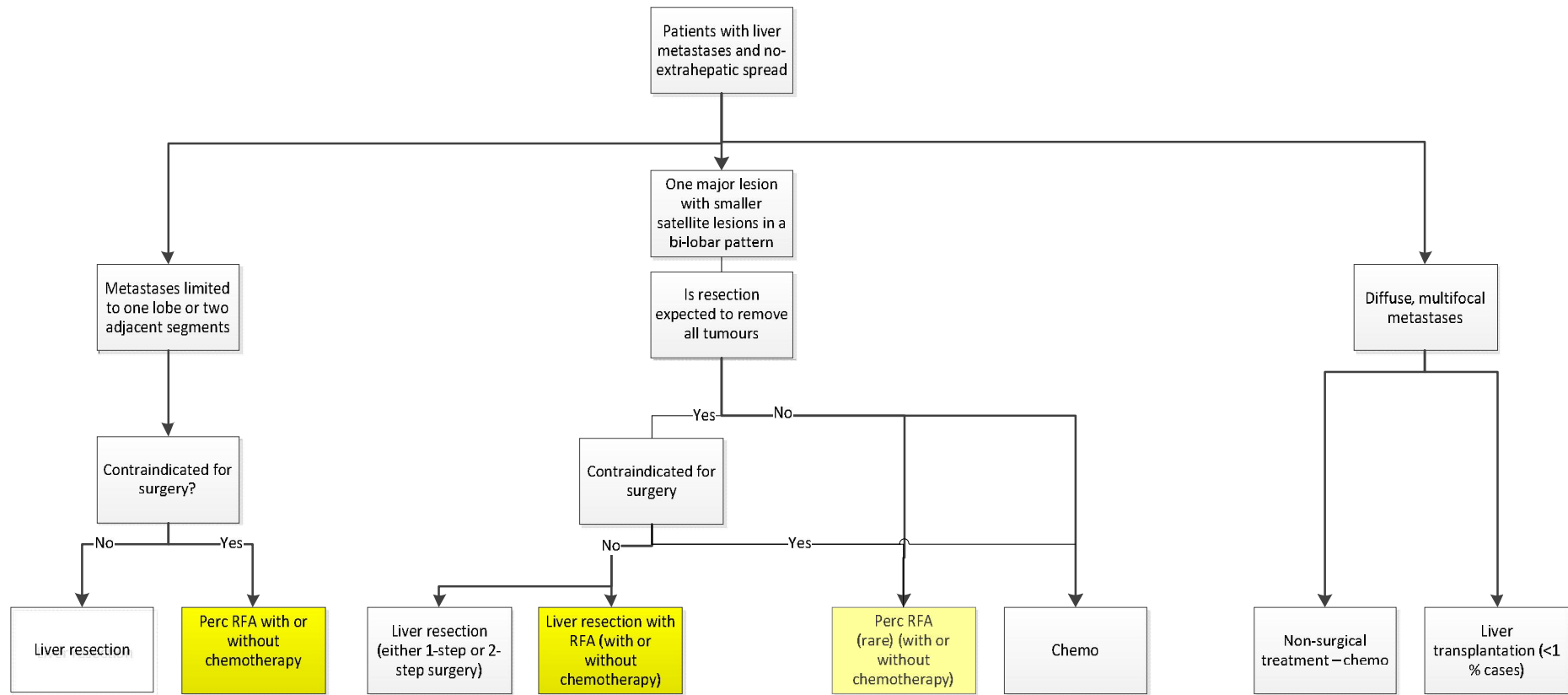
Figure 4   Current clinical practice for patients with secondary unresectable liver lesions (Population 2)

Chemo = chemotherapy; perc = percutaneous; RFA = radiofrequency ablation
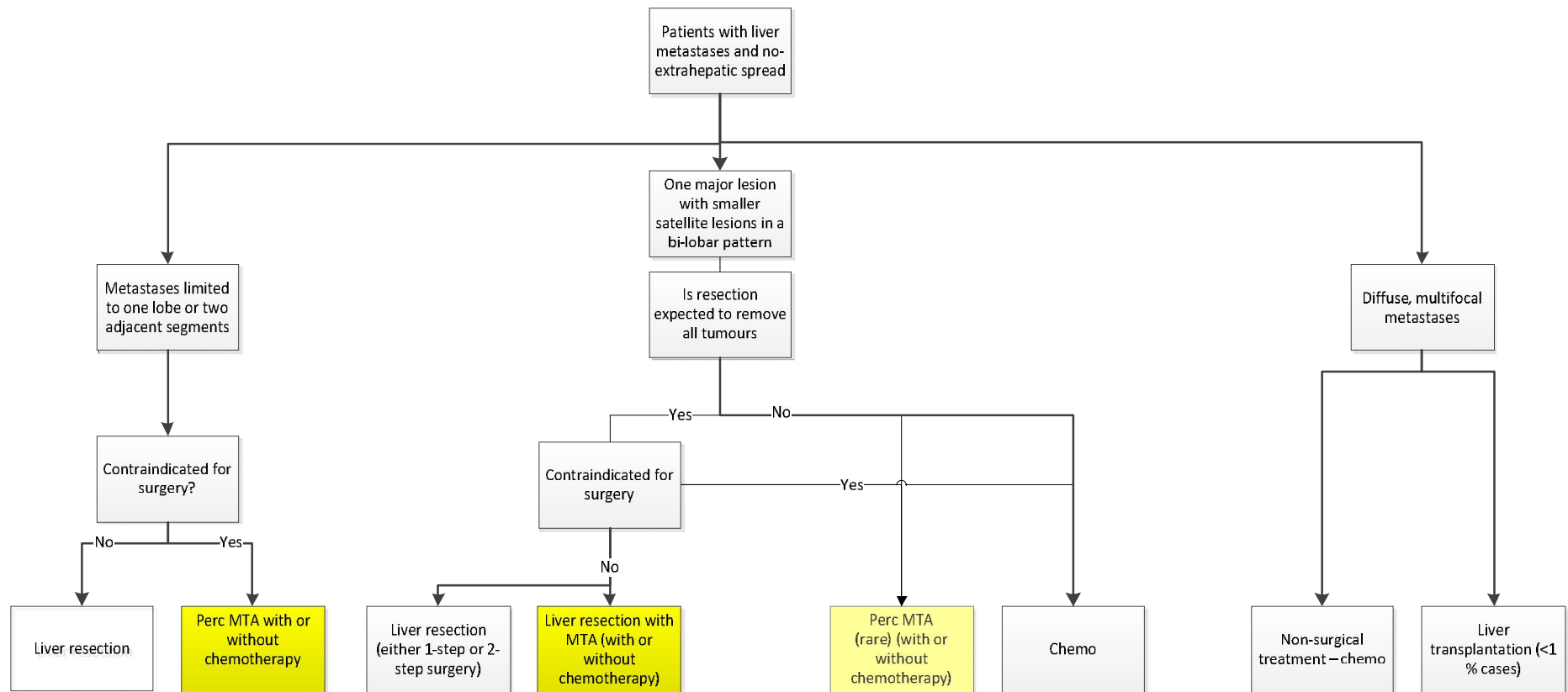
Figure 5   Proposed clinical practice for patients with secondary unresectable liver lesions (Population 2)

Chemo = chemotherapy; MTA = microwave tissue ablation; perc = percutaneous;
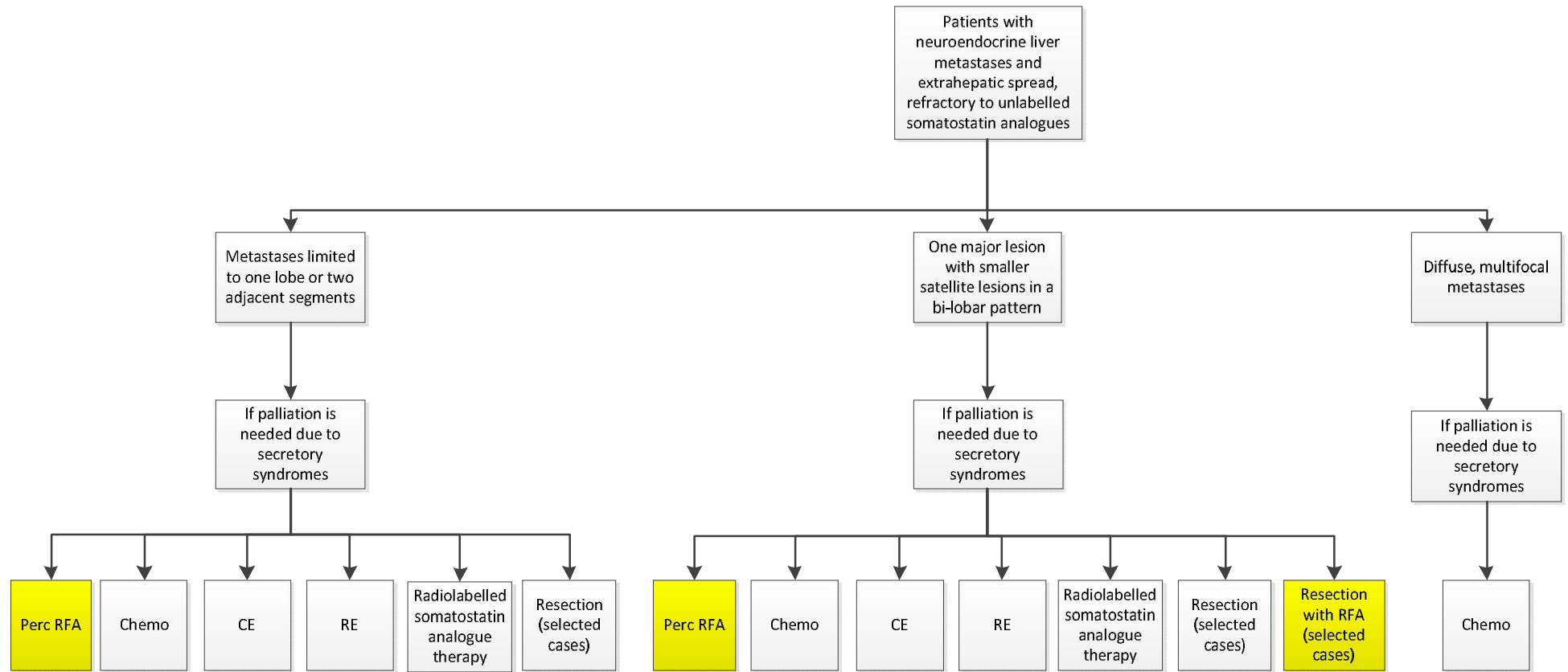
Figure 6   Current clinical practice for patients with unresectable neuroendocrine liver metastases who are refractory to somatostatin analogue therapy (Population 3)

CE = chemoembolization; chemo = chemotherapy; perc = percutaneous; RE = radioembolisation; RFA = radiofrequency ablation
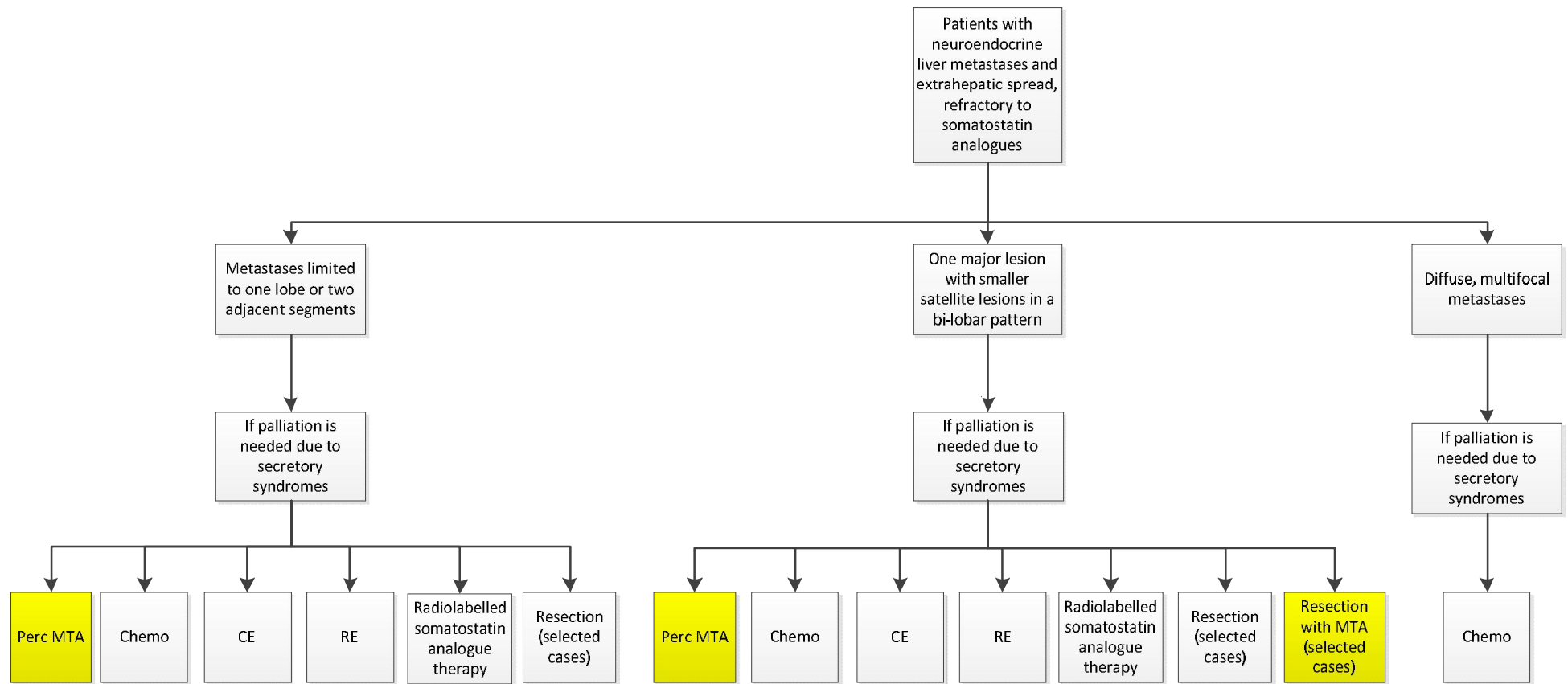
Figure 7　Proposed clinical practice for patients with unresectable neuroendocrine liver metastases who are refractory to somatostatin analogue therapy (Population 3)

APPENDIX C   SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period
Cochrane Library—including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	01 01 1990 – 10 5 2016
Current Contents	01 01 1990 – 10 5 2016
EMBASE	01 01 1990 – 10 5 2016
PubMed	01 01 1990 – 10 5 2016
Web of Science—Science Citation Index Expanded	01 01 1990 – 10 5 2016
Econlit	01 01 1990 – 10 5 2016
Scopus	01 01 1990 – 10 5 2016

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
NHMRC—National Health and Medical Research Council (Australia)	<www.nhmrc.gov.au/>
Current Controlled Trials Meta Register	<http://controlled-trials.com/>
International Network of Agencies for Health Technology Assessment	<www.inahta.org/>
Australian and New Zealand Clinical Trials Registry	<www.anzctr.org.au>
US National Institutes of Health Clinical Trials Registry	<clinicaltrials.gov>
Pearling: all included articles will have their reference lists searched for additional relevant source material	(Not applicable)

SPECIALTY WEBSITES

American Gastroenterological Association	<www.gastro.org/>
American College of Gastroenterology	<http://gi.org/>
Gastroenterological Society of Australia	<www.gesa.org.au/>
American Association for the Study of Liver Diseases	<www.aasld.org/>

Table 59   Profiles of systematic reviews comparing MTA and RFA in patients with primary liver tumours (Population 1) included in this assessment

Author Year Country Quality	Included studies *K* studies *N* patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Statistical analysis	Outcomes assessed Duration of follow-up Subgroup analysis	Comments
Facciorusso et al (2016) Italy Quality: high	*K* = 7 *N* = 774 Study designs: RCT × 2 RCCC × 1 RHCC × 4 Recruitment period range: 1997–2013 Population range (*N*): 53–198 <u>Objectives</u> Comparison and meta-analysis of RFA and MTA for HCC	Patients with HCC tumours with mean size 1.6–2.9 cm and within Child–Pugh B score, except for Ohmoto et al (2009), in which patients were primarily Child–Pugh A class	<u>Inclusion</u> RCT, CCoh, studies comparing RFA and MTA <u>Exclusion</u> Non-human & non-English studies; CS, abstracts and studies with insufficient data	<u>Intervention</u> Percutaneous MTA <u>Comparator</u> Percutaneous RFA	Two-group comparison fixed-effects models—Mantel–Haenszel test Random-effects models—Der-Simonian and Laird test Heterogeneity—Cochrane's χ^2 test and I^2 statistic ($P < 0.1$ significant) Between-study heterogeneity—subgroup analyses ($P < 0.1$ significant) Publication bias—funnel plots, Begg and Mazumdar test	<u>Primary</u> Complete response Local recurrence rate <u>Secondary</u> Tumour response Survival (3 year) Major complications	5 included studies were conducted mainly in Asia, and 2 in Egypt
Chinnaratha et al (2016) Australia Quality: high	*K* = 10 *N* = 1,298 Study designs: RCT × 1 NRPC × 2 RCCC × 1 RHCC × 6 Population range (*N*): 42–198 Objectives	Patients with HCC; mean tumour size 2–3 cm for most studies	<u>Inclusion</u> Participants: adults with either very early stage[a], early stage, or multifocal/large HCC; study designs: RCTs. Prospective or retrospective cohorts <u>Exclusion</u> None reported	<u>Intervention</u> Percutaneous RFA <u>Comparator</u> Percutaneous MTA	Random-effects model—Der-Simonian and Laird method Difference in follow-up adjustment—meta-regression analysis Inter-study heterogeneity—χ^2 (with thresholds: I^2 statistic > 50% and $P < 0.1$) Publication bias—funnel plots	<u>Primary</u> Risk of local tumour progression <u>Secondary</u> Complete ablation rates OS Major adverse events <u>Subgroup analysis</u> (primary outcome only) Study quality	Abstracts from the AASLD and EASL meetings for the years 2012 and 2013 were reviewed for inclusions

Author Year Country Quality	Included studies K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Statistical analysis	Outcomes assessed Duration of follow-up Subgroup analysis	Comments
	To compare effectiveness and safety of RFA and MTA for the treatment of primary HCC					Tumour stage Mean follow-up period 5–45 months	
Huo and Eslick (2015) Australia Quality: moderate	K: 16 N = 2,062 Study designs: RCT × 2 NRPC × 7 RHCC × 2 RCCC × 5 Objectives To evaluate and meta-analyse the efficacy and safety of MTA vs RFA based on the results of published retrospective and prospective studies	Patients with HCC or metastatic liver tumours N = 2,062 MTA group Mean age: 57.8 y Mean tumour size: 26 mm Mean nodule N: 1.22 RFA group Mean age: 59.2 y Mean tumour size: 26 mm Mean nodule N: 1.00	Inclusion Diagnosed HCC or confirmed liver metastases; RCTs or non-RCTs; data on at least 1 year OS, local recurrence rate, complete ablation or disease-free survival Exclusion Animal studies; duplicate publications or studies previously identified	Intervention MTA Cooled-tip MTA used in 53% of trials (8 of 15, the remainder used non-cooled tip 45–100 W Comparator RFA Cooled-tip RFA used in 57% of trials (8 of 14), the remainder used expandable tip 60–200 W	Pooled ORs and 95% CIs Cochran Q statistic and I^2 for heterogeneity Egger regression model for publication bias Analyses performed with Comprehensive Meta-analysis (v 2.0; Biostat, Englewood, NJ, USA) for Windows (Microsoft, Redmond, WA, USA)	OS Disease-free survival Local recurrence rate Complete ablation Adverse events Costs Subgroup analysis HCC Liver metastases Ablation equipment Ablation time Milan criteria Follow-up range 10–137 months	MTA and RFA were not specified as percutaneous, laparoscopic or surgical
ASERNIP-S (2006) Australia Quality: high	K = 5 N = 303 Study designs: RCT × 1 RHCC × 4 Objectives To assess new studies for safety and effectiveness of RFA for primary HCC or CRLM	Patients with either HCC or CRLM	Inclusion Patients with HCC or CRLM Exclusion Patients with additional disease other than recurrent liver disease	Intervention RFA Comparator MTA	Pooling not considered appropriate RR and WMD and 95% CIs were calculated individually for the same outcomes across included RCTs Calculations performed with RevMan 4.2 (Update Software Ltd 2000)	Sessions required Therapeutic response Local recurrence Survival Disease-free survival Complete ablation rate Major complications Cause of death Procedure time	Other comparators were included but not considered for this review: surgical resection, HAIC, PEI, cryoablation, LITT

Author Year Country Quality	Included studies K studies N patients (total) Objectives	Population characteristics	Eligibility criteria	Intervention Comparator	Statistical analysis	Outcomes assessed Duration of follow-up Subgroup analysis	Comments
	in comparison with other techniques, as an update to an earlier review						

AASLD = American Association for Study of Liver Disease; CCoh = comparative cohort; CI = confidence interval; CRLM = colorectal liver metastases; CS = case series; EASL = European Association for Study of Liver; HAIC = hepatic arterial infusion chemotherapy; HCC = hepatocellular carcinoma; LITT = laser-induced thermotherapy; MTA = microwave tissue ablation; OS = overall survival; WMD = weighted mean difference; MTA = microwave tissue ablation; N = number; OR = odds ratio; NRPC = non-randomised prospective comparison; PEI = percutaneous ethanol injection; RCCC = retrospective concurrent control cohort; RCT = randomised controlled trial; RFA = radiofrequency ablation; RHCC = retrospective historical control cohort; RR = relative risk

[a] Very early stage, single tumour ≤2 cm; early stage, single tumour or up to 3 nodules, each ≤3 cm; multifocal/large HCC, outside Milan criteria but without vascular invasion or extrahepatic metastases (Chinnaratha, M. A. et al 2016)

Table 60   Profiles of comparative studies of MTA vs RFA in patients with primary liver tumours (Population 1) included in this assessment

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
Chinnaratha et al (2015) Australia	Multicentre RHCC Recruitment: Jan 2006 – Dec 2012 Level III-3 Quality: moderate	N = 126 Patients treated with RFA: N = 101 (80.2%) Patients treated with MTA: N = 25 (19.8%) Mean age ± SD: 62.1 ± 10.4 y Male/female: 98/28 Child-Pugh class A/B/C: 92/23/2 Cirrhosis present/ not present: 117/9	Inclusion Consecutive patients for initial HCC treatment with curative intent; single nodule ≤5 cm or up to 3 nodules ≤3 cm Exclusion Previous local therapy; PTA for local tumour control on a liver transplant waiting list; known extrahepatic metastasis or microvascular invasion Objectives To assess local tumour progression following PTA and the factors predicting HCC recurrence	MTA Percutaneous (adopted as preferred modality in 2011 and 2012) Acculis MTA System (Microsulis Medical Ltd, Hampshire, UK), 2.45 GHz, up to 140 W Applicator was Accu2i pMTA (Microsulis Medical Ltd) with 16 mm active tip, 1.8 mm diameter and 14 or 19 cm disposable microwave antenna Duration and power determined by treating radiologist	RFA Percutaneous (RFA used from 2006 until MTA took over as preferred modality) Radionics Cool Tip System (Radionics, Burlington, MA, USA) Disposable 17-gauge straight single electrode with 3 cm active tip Up to 200 W Burn cycle of 12 min, tailored to each lesion, with max. individual burn radius of 3 cm	Outcomes Overall recurrence-free survival Local tumour recurrence-free survival Overall IHR[d] Number of sessions required for complete ablation Adverse events Statistical analyses Multivariate analysis to identify predictors of progression IBM SPSS v 19.0 (IBM Corp., Armonk, NY, USA) $P < 0.05$ was significant Duration of follow-up 1, 2, and 3 years	Patients who underwent MTA or RFA were from different time periods, as treatment centres switched their preferred ablation modality

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
Ding et al (2013) China	RCCC Level III-2 Quality: moderate	N = 879 Population included: HCC—N = 770 CAC—N = 24 Metastatic—N = 85 Male/female: 674/205 Mean age (range): 58.29 (25–92) y	Inclusion Patients not suitable for surgical resection or who refused surgical resection; tumour size ≤6 cm; 4 or fewer tumours Exclusion Signs of invasion of the intrahepatic vessels, the main branches of the bile duct or the inferior vena cava Objectives To retrospectively investigate the common complications of thermal ablation of liver tumours by RFA and MTA	MTA MTC-3 microwave therapy instrument (Forsea Microwave & Electronic Research Institute, Nanjing, China) 2450 MHz, 40–80 W The antenna was a 14-gauge unipolar cooled-shaft needle 15 cm in length and a 1.5 cm long active tip	RFA Cool-tip RFA system (Radionics, Burlington, MA, USA) 480 kHz, 200 W The electrode was a unipolar needle with 15–20 cm length and 2–3 cm exposed tip, cooled by internal circulation of 0 °C distilled ice water via a pump	Outcomes Major complications[a] Minor complications Statistical analysis Comparison of categorical variables: χ^2 test or Fisher's exact test Continuous data: expressed as mean ± SD Analysis was performed using SPSS for Windows v 11.5 (SPSS, Chicago, IL, USA) $P < 0.05$ was significant Duration of follow-up 6–75 months	Percutaneous or intraoperative ablation was performed. Surgical approach may have been used as part of a treatment plan for partial liver resection or other procedures For percutaneous ablation, 2 US systems were used for guidance and monitoring: Philips IU-22 (Philips, Bothell, WA, USA) and Aloka 500 (Aloka, Tokyo, Japan) with 1–5 MHz convex array probe. For surgical approach, the Aloka 5000 and α10 and probes at 5–10 MHz were used
Lee et al (2016) China	Single-centre RHCC Recruitment: May 2003 – Jan 2011 Level III-3 Quality: moderate	MTA group N = 26 Age (range): 62.5 (49–79) y Male/female: 19/7 Child's grade A/B: 23/3 RFA group N = 47 Age (range): 58 (43–77) y Male/female: 40/7	Inclusion Consecutive patients with HCC diagnosis; lesions 2–6 cm; unresectable tumour or resectable or patient preferred local ablation to hepatectomy; tumour not feasible for percutaneous RFA Exclusion Macroscopic vascular bile duct invasion; patients with >2 tumours; tumours >6 cm	MTA Laparoscopic or laparotomy 2.45 GHz machine (Microsulis Medical Ltd, Hants, UK) Microantenna 5 mm	RFA Laparoscopic or laparotomy Cool-tip RFA needle (Covidien, Fridley, MN, USA) or LeVeen needle (Boston Scientific, Natick, MA, USA)	Outcomes Recurrence-free survival OS Statistical analyses Comparison of categorical variables used Fisher's exact test Survival calculated using the Kaplan–Meier method and compared with log-rank test $P < 0.05$ was significant Duration of follow-up	Recurrent tumour after previous treatment was not considered a contraindication to MTA Evaluation at follow-up was conducted using CT

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		Child's grade A/B: 42/5	Objectives To compare RFA and MTA by surgical approach			1 month, then 3-monthly during first 2 y, 6-monthly after 2 y	
Potretzke et al (2016) USA	Single-centre RHCC Recruitment: 2001–2013 Level III-3 Quality: moderate	RFA *N* = 55 Mean age (range): 32 (23–88) y Male/female: 40/15 MTA *N* = 99 Mean age (range): 61 (44–82) y Male/female: 81/18	Inclusion All patients who underwent percutaneous RFA or MTA between 2001 and 2013 for HCC Exclusion Patients who underwent TACE in combination with thermal ablation, or who underwent prior chemotherapy for HCC Objectives To compare local treatment of HCC efficacy and major complications between RFA and MTA systems	RFA Percutaneous under general anaesthesia Internally water-cooled electrode and generator (Cool-tip; Covidien, Boulder, CO, USA) with single, cluster, or multiple electrodes in switched mode (Cool-tip Switching Controller; Covidien)	MTA Percutaneous under general anaesthesia High-powered gas-cooled system with continuous in-phase output to up to 3 antennae (Certus 140; Neu-Wave Medical, Inc, Madison, WI, USA)	Outcomes Local tumour progression OS Complications Statistical analyses Kaplan–Meier compared with log-rank test for survival Cox's proportional hazard model for risk differences Fine and Gray for risk analyses Statistics performed with R 3.1.0 (R Core Team, 2014 R Foundation for Statistical Computing, Vienna, Austria) Duration of follow-up Every 3 months for 1 y; 6-monthly thereafter Median follow-up: RFA—31 (1–148) months; MTA—24 (1–57) months	RFA was used on all patients treated before 2011. All patients were treated with MTA from 2011 to 2013

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
Simo et al (2011) USA	Single-centre RHCC Recruitment: 2006–2008 Level III-3 Quality: moderate	MTA N = 13 Mean age (range): 59.6 (49–72) y Male/female: 7/6 Child's class A/B/C: 7/6/0 RFA N = 22 Mean age (range): 58 (45–79) y Male/female: 19/3 Child's class A/B/C: 12/7/3	Inclusion All patients with lesion not amenable to percutaneous ablation owing to position of tumour; not candidates for resection owing to hepatic dysfunction, portal hypertension or other comorbidities Exclusion NR Objectives To analyse initial experience with laparoscopic MTA compared with other modalities	Laparoscopic MTA Performed by single primary surgeon Single or double antennae at 915 Hz, 45 W (VivaWave System, Valleylab, Boulder, CO, USA)	Laparoscopic RFA Performed by single primary surgeon Appropriate probe size used as per manufacturer's instructions (Boston Scientific Corporation, Natick, MA, USA)	Outcomes Mortality Morbidity Technical success Operative time Local tumour control Disease progression Statistical analysis STATA (v 10.0, College Station, TX, USA) Group comparisons used Student's t-test, χ^2 test or OR analysis $P < 0.05$ was significant Mean follow-up (range) MTA: 7 (2.5–10.5) months RFA 19 (1.5–31) months	MTA was first used in 2008 The OS and disease-free survival were not reported in this assessment as follow-up time was considerably different between the 2 groups and they were therefore deemed incomparable
Sakaguchi et al (2009) Japan	Multicentre RCCC Recruitment: 1994–2005 Level III-3 Quality: poor	MTA N = 142 Mean age (± SD): 64.9 ± 7.8 y Male/female: 107/35 Child-Pugh class A/B/C: 86/56/0 RFA N = 249 Mean age (± SD): 65.6 ± 8.9 y Male/female: 169/80	Inclusion All patients who underwent endoscopic (laparoscopic or thoracoscopic) MTA or RFA for solitary HCC Exclusion NR Objectives To compare MTA and RFA in patients with solitary HCC receiving endoscopic ablation and to assess factors affecting survival	Endoscopic MTA Laparoscopy or thoracoscopy	Endoscopic RFA Laparoscopy or thoracoscopy	Outcomes Survival Local recurrence Complications Statistical analyses Log-rank test, Fisher's exact-test and χ^2 test for group differences Cox's proportional HR model for effects of survival or recurrence Kaplan–Meier method for survival $P < 0.05$ was significant	-

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		Child-Pugh class A/B/C: 147/98/4				<u>Follow-up</u> NR	

CCA = cholangiocarcinoma; CT = computed tomography; HCC = hepatocellular carcinoma; HR = hazard ratio; IHR = intrahepatic recurrence; MTA = microwave thermal ablation; NR = not reported; OR = odds ratio; OS = overall survival; PTA = percutaneous thermal ablation; RCCC = retrospective concurrent control cohort; RFA = radiofrequency ablation; RHCC = retrospective historical control cohort; SD = standard deviation; SPSS = Statistical Package for Social Sciences; STATA = data analysis and statistical software for professionals; TACE = transcatheter arterial chemoembolisation; US = ultrasound

[a] Major and minor complications were assessed according to the Society of Interventional Radiology (SIR) grading system. The definition of a major complication is an event that leads to substantial morbidity and disability, increasing level of care, or hospital admission or substantially lengthened hospital stay (SIR classifications C–E). All other complications were considered minor.

[b] Criteria for ineligibility for resection were major resection in Barcelona Clinic Liver Cancer A2–A3–A4 disease; technical contraindications; or major resection in patients with Model for End-stage Liver Disease (MELD) score of >10. Criteria for ineligibility for percutaneous ablation were critical location (proximity to gastrointestinal tract or bladder or major hepatic vessels, superficial or exophytic nodules); untreatable ascites; or severe coagulopathy (prothrombin time of <40% and/or platelet count of <30 × 10^9/L)

[c] Criterion for severe liver decompensation was MELD score of >20 or Child-Pugh class C. Criterion for large multinodular HCC was nodule size of >7.0 cm or >5 nodules.

[d] IHR (intrahepatic recurrence) is composed of both local tumour progression and intrahepatic distant recurrence (new HCC nodule remote from ablative lesion)

Table 61   Profiles of comparative studies of MTA vs RFA in patients with secondary liver tumours (Population 2) included in this assessment

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
Liu et al (2013a) China	Single-centre NRPC Level III-2 Quality: moderate	N = 89 <u>MTA group</u> N = 35 Age ± SD: 53.4 ± 15.3 y Male/female: 21/14 Primary tumour CRC/other: 16/19 <u>RFA group</u> N = 54 Age ± SD: 53.1 ± 12.7 y Male/female: 33/21	<u>Inclusion</u> Patients with liver metastases; <5 lesions; tumour diameter ≤5 cm <u>Exclusion</u> Patients with extrahepatic metastases or vascular invasion <u>Objectives</u> To evaluate the therapeutic effects and complications of thermal ablation in patients with liver metastases	MTA ECO-100C microwave generator (ECO Microwave Electronic Institute, Nanjing, China) and a FORSEA MTC-3C microwave system (Qinghai Microwave Electronic Institute, Nanjing, China) at 2450 MHz, 0–150 W 14-gauge cooled-shaft electrode	RFA Before Sept 2004: RF 2000 system (RadioTherapeutics, Mountain View, CA, USA); needle electrode with 15-gauge insulated cannula and 10 hooked tines; 10–90 W After Sept 2004: 375 kHz generator (Elektrotom HiTT 106; Berchtold Medizinelektronik, Germany);	<u>Outcomes</u> Local recurrence Distant recurrence Survival Major complication Complete ablation <u>Statistical analysis</u> Comparison of categorical variables with χ^2 test or Fisher's exact-test For continuous variables, Student's t-test $P < 0.05$ was significant	All patients were either not amenable or refused to receive surgical resection Patients were monitored using US, CT or MRI

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Comparator	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		Primary tumour CRC/other: 22/32			open-perfused electrode 15 cm, 14-gauge; single application at 60 W for 8 min	Survival analysis used the Kaplan–Meier method Statistics were analysed in SPSS 16.0 (SPSS Inc, Chicago, IL, USA) <u>Duration of follow-up</u> Mean follow-up period 32.2 months	
Hompes et al (2010) Belgium	Historical matched control study Level III-3 Quality: Poor	<u>MTA group</u> N = 6 Median age (range): 64 (47–82) y Male/female: 2/4 Primary tumour: lung N = 1 Hepatopancreatic duct N = 1 CRC N = 4 <u>RFA group</u> N = 13 Median age (range): 58 (35–70) y Male/female: 7/6 Primary tumour: Cervix N = 1 CRC N = 12	<u>Inclusion</u> Patients with metastatic tumours <3 cm not suitable for surgery; CRLM patients with clinical risk score ≥3 and minimal response to systemic chemotherapy and with severe systemic disease <u>Exclusion</u> Underlying liver disease <u>Objectives</u> To evaluate the variability and reproducibility of ablation diameters after single-probe MTA vs RFA on matched tumours from a database	MTA Laparoscopic in 5 and percutaneous in 1 patients Single cooled antenna 22 cm long and 3.7 cm active tip (VT2237); 915 MHz Valleylab MW ablation generator (VTSYS3; Covidien, Europe); applied for 10 min at 40 W	RFA Laparoscopic in 7, surgical in 4 and percutaneous in 2 patients Monopolar 200 W RFA generator; single cool-tip laparoscopic electrode 25 cm long with 3 cm activating tip (Covidien, Radionics Europe NV); applied for 15 min	<u>Outcomes</u> Tumour diameter pre- and postoperative Local recurrence <u>Statistical analysis</u> Measurements were compared with Mann–Whitney U-test Linear model with logarithmic transformations were used to compare changes SAS v 9.2 software P < 0.05 was significant <u>Duration of follow-up</u> 1 week 3 months	Patients were included with primary disease of different location

CRC = colorectal cancer; CRLM = colorectal liver metastases; CT = computed tomography; MRI = magnetic resonance imaging; MTA = microwave thermal ablation; NRPC = non-randomised prospective comparison; RFA = radiofrequency ablation; SAS = Satistical Analysis System; SD = standard deviation; SPSS = Statistical Package for Social Sciences; US = ultrasound

Table 62   Profiles of case series of MTA in patients with primary or secondary liver tumours (Population 1 or 2, or both) included in this assessment

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
Liang et al (2009) China	Case series (retrospective database analysis) Level IV Quality: Moderate	Total N = 1136 Pop 1: N = 879 patients Pop 2: N = 257 patients Total population Male/female: 902/234 Mean age (± SD): 54.48 (± 11.36) y Child–Pugh class B/C: 75%/5%	Inclusion Single tumour ≤8 cm; ≤7 tumours in total; absence of portal vein thrombosis; general condition would permit; treatment between May 1994 and May 2007 Exclusion Portal vein thrombosis; patients with ascites and prothrombin time of >40 s Before 2005, only patients with tumours ≥5 mm away from bile duct, gallbladder and bowel were enrolled, but after 2005, the 5 mm restriction was reduced Objectives To report complications of MTA for the treatment of liver cancer and to determine the possible risk factors	MTA Percutaneous Before 2005 (n = 583): Uncooled-shaft system 2005 onwards (n = 553): Cooled-shaft system (KY-2000; Kangyou Medical Instruments, Nanjing, China) Both systems used 21-gauge thermocouple needles	Outcomes Major complications Minor complications and side-effects Mortality Statistical analysis χ^2 test to determine associations Mann–Whitney U-test for variance SPSS 14.0 (Chicago, IL, USA) P < 0.05 was significant Follow-up At time of death, liver transplantation or last clinical visit before 30 Nov 2007	Treatment options were determined with consensus of a panel of experienced specialists
Livraghi et al (2012) Italy	Case series Level IV Quality: moderate	N = 187 patients with metastases from CRC Male/female: not reported Mean age: not reported	Inclusion Patients treated in 14 centres in Italy who had: Disease limited to liver Operable nodules ≤2 cm Inoperable nodules 2–5 cm <3 lesions No substantial coagulopathy However, lesions >5 cm or >3 in number could be treated at centre's discretion	MTA Percutaneous, laparoscopic or open, using cool-shaft MTA (AMICA-GEN, HS Hospital Service SpA, Aprilia, Italy), with 'mini-choke' 2.45 MHz, 60–100 W Ablation time 5–15 min	Outcomes Major complications Minor complications Side-effects Statistical analysis None undertaken Follow-up 1 month, every 3–4 months	-

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
			Objectives Report complications encountered by members of a collaborative group performing MTA in patients with focal liver cancer			
Shimada et al (1998) Japan	Case series Level IV Quality: moderate	N = 29 Male/female: 21/8 Mean age not reported for whole group; 56.9–62.7 y	Inclusion and exclusion criteria not reported Objectives Describe complications encountered using MTA	MTA Open (n = 23) or percutaneous (n = 6) approach, using Microtase (Nippon Shoji, Osaka, Japan) 2450 MHz, 100 W for open and 60 W for percutaneous Ablation time 60 s	Outcomes Complications Statistical analysis None undertaken Follow-up 11–55 months	Old study
Ierardi et al (2013) Italy	Case series Level IV Quality: moderate	N = 25 Metastases from: CRC: 21 Breast: 2 Pharynx: 1 Oesophagus: 2 Retroperitoneal leiomyosarcoma: 1 Gallbladder: 2 Renal: 1 Pancreatic: 1 Male/female: 17/8 Mean age (range): 65.9 (49–83) y	Inclusion Absence of or stable extrahepatic disease Inoperable lesions Tumour size >3 cm Lesions located near vessels with diameter >3 mm Exclusion Surgically treatable lesions or amenable to RFA (not described) Objectives To evaluate the technical success, effectiveness and safety of MTA to overcome the limits of RFA	MTA: Percutaneous MTA (Evident, Covidien, USA) 915 MHz, 45 W Antenna 14.5-gauge (Evident MW Ablation Percutaneous Antenna), continuously perfused with saline solution to avoid possible thermal damage All lesions treated with 2 or 3 antennae simultaneously Total ablation time 10 min	Outcomes Technical success, disease-free survival, safety and efficacy Statistical analyses Kaplan–Meyer method for evaluation of survival Duration of follow-up Mean 12.04 months (range 3–36 months)	-
Liang et al (2003) China	Case series Level IV Quality: poor	N = 74 Metastases from: CRC: 28 Gastric/cardiac: 12	Inclusion None specified Exclusion None specified	MTA Ultrasound-Guided Microwave Coagulator-I (PLA General Hospital and Insti-	Outcomes Survival, complications Statistical analyses Survival rates calculated using	16 patients eligible for resection elected to have MTA

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		Breast: 11 Lung: 12 Pancreatic: 1 Gallbladder: 2 Renal: 5 Ocular melanoma: 1 Small bowel leiomyosarcoma: 2 Male/female: 44/30 Age (range): 27–81 y (no mean reported)	Objectives To examine predictors of survival in patients undergoing MTA for liver metastases	tute 207 of the Aerospace Industry Company, Beijing, China) 2450 MHz, 10–80 W	Kaplan–Meier method; predictive factors compared with log-rank test; multivariate Cox's proportional hazards model Duration of follow-up Mean 25.1 ± 11.4 months, range 5–83 months	
Abe et al (2005) Japan	Case series Level IV Quality: moderate	N = 8 All breast metastases All female Mean age (range): 49.0 (41–69) y	Inclusion Limit of 5 lesions in each patient Lesions <3 cm diameter Exclusion Major coagulation disorders and hepatic failure Objectives To evaluate the efficacy of MTA for local control of liver metastases from breast cancer	MTA Microwave coagulator (Microtase, OT-110M, Osaka, Japan) 2.45 GHz, 60 W Ablation duration 60 s, usually 3 ablations at each point MRI guided	Outcomes Treatment efficacy, side-effects, complications Statistical analyses None undertaken Duration of follow-up Mean 25.9 months (range 1–43 months)	4 patients had only liver metastases, 4 had liver and other metastases Focus of paper was on imaging rather than intervention
Li et al (2013) China	Case series Level IV Quality: moderate	N = 18 Nasopharyngeal metastases Male/female: 15/3 Mean age (range): 45.7 (31–61) y Single metastasis in n = 14, 2 metastases in n = 3, 4 metastases in n = 1	Inclusion Karnofsky performance status >80 Max 5 liver lesions Failure of previous chemotherapy or ineligible for chemotherapy Local control of primary tumour by radiation therapy Local control or absence of extrahepatic metastases Exclusion	MTA Percutaneous MTA (FOR-SEA, Qinghai Microwave Electronic Institute, Nanjing, China) 14-gauge cooled-shaft antenna Power 50–60 W Cumulative ablation time 4–12 min	Outcomes Survival; complications Statistical analyses Kaplan–Meier survival curves Duration of follow-up 22.4 months (range 4–52 months)	-

Author Year Country	Study design Level of evidence Quality appraisal	Population charac- teristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		n = 2 patients also had bone metastases	Coagulation disorders or liver failure Objectives Report of institutional experience and outcomes			
Liang et al (2014) Taiwan	Case series Level IV Quality: poor	*n* = 13 all CRC metastases Male/female: 7/6 Mean age: 69.2 ± 9.08 y Mean tumour size (cm): 5.31	Inclusion Unresectable tumours or refused surgery Tumours 4–7 cm diameter Exclusion None described Objectives Evaluate safety and efficacy of novel MTA system in cancers exceeding 4 cm	MTA Open = 10 Laparoscopic = 3 (MedWaves AveCure MWA system, San Diego, CA, USA) 902–928 MHz, 10–32 W No of sessions, mean ± SD: 2.23 ± 0.73 Time, mean ± SD: 1823 ± 641.8 s	Outcomes Ablation success, recurrence, complications Statistical analyses None undertaken Duration of follow-up Mean 16.5 months	Included primary cancer patients but provided separate results
Martin et al (2007) USA	Case series Level IV Quality: moderate	*N* = 20, 67 tumours HCC = 5 Metastases from CRC = 10 Carcinoid = 2 Ovarian = 1 Breast = 1 Gastric = 1 Male/female: 13/7 Median age (range): 65 (46–83) y	Inclusion Liver tumours amenable to complete ablation or combination of resection and ablation 18+ years Exclusion Metastases amenable to resection alone Tumour >7 cm Objectives To evaluate safety, operative time, rate of complete ablation and local recurrence	Open or laparoscopic MTA (Vivant Medical microwave system, Mountain View, California, USA) 915 MHz Mean ablation time 10 min (5–40 min) Median operative time 106 min (47–249 min)	Outcomes Ablation success, recurrence, complications Statistical analysis None undertaken Duration of follow-up Median 19 months (range 5–23 months)	9/20 patients underwent additional procedures such as partial hepatec- tomy, colectomy and gastrectomy
Li et al (2012) China {Also includes	Case series Level IV Quality: moderate	*N* = 49; 61 lesions Lesions from: CRC = 18	Inclusion Unresectable tumour or resection refusal	Percutaneous MTA (KY-2000, Kangyou Medical, Nanjing, China)	Outcomes Complete ablation, local recur- rence	Following up outcomes of MTA in pop 2 was not the aim of this study; it

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
pop 1 data}		Gynaecologic = 13 Breast = 10 Gastric = 9 Lung = 8 Prostate = 2 Oesophageal = 1 Male/female: not reported by cancer type Age: not reported by cancer type	Tumour accessible via percutaneous approach ≤3 hepatic lesions with max diameter of 4 cm Absence or portal vein thrombosis or extrahepatic metastases Prothrombin time of <25 s Prothrombin activity >40% Platelet count >40 cells × 10^9/L Exclusion New lesions found after previous MTA, TACE, RFA or other therapy Also received immunotherapy Lost to follow-up Objectives To compare patients undergoing MTA at sites close to and further away from the diaphragm. Some data are provided for outcomes relevant to pop 2	2450 MHz, 1–100 W Cool-shaft antenna Max 3 sessions Total treatment time 180–1840 s	Statistical analyses None undertaken Duration of follow-up Not reported separately for pop 2; for 2 groups compared in the study (close to and further from diaphragm), follow-up was 11.5 ± 10.3 months and 12.7 ± 9.6 months, respectively	provided some data so has been included on that basis
Alexander et al (2015) USA {Also includes pop 1 data}	Case series Level IV Quality: moderate	N = 39 Metastases from: CRC = 27 Breast = 4 Carcinoid = 2 Lung = 2 Melanoma = 2 CCA = 1 Anal = 1 Mean age ± SD: CRC group: 68.4 ± 2.4	Inclusion Single liver neoplasm Refused or not suitable for resection Exclusion Radiographic evidence of nodal disease Adenopathy Extrahepatic disease International normalised ratio of >1.8 on day of ablation Objectives	MTA Percutaneous or intraoperative Five different machines used: either 915 MHz (Evident, Covidien, USA' Micro-ThermX, BSD Medical, USA; AveCure, MedWaves, USA) or 2450 MHz (Certus 140, NeuWave, USA; Amica, Hospital Service, Italy)	Outcomes Survival Statistical analyses Kaplan–Meier analysis Duration of follow-up: Not reported, but results provided for survival at 1 year	Some patients also had resection, but numbers not reported

Author Year Country	Study design Level of evidence Quality appraisal	Population characteristics	Eligibility criteria Objectives	Intervention	Outcomes assessed Statistical analyses Duration of follow-up	Comments
		y Other: 68.6 ± 3.7 y Male/female: not reported by cancer type	Evaluate safety and efficacy of MTA in treating solitary primary and metastatic liver tumours	Cooled-shaft antennae		
Yu et al (2015) China {Also includes pop 1 data}	Case series Level IV Quality: moderate	N = 307 Metastases from: Gastrointestinal = 387 Breast = 47 Lung = 44 Pancreas = 38 Extrahepatic CCA = 37 Ovarian = 26 Other = 74 Male/female not reported for pop 2 Age not reported for pop 2	Inclusion Single lesion ≤8 cm ≤3 lesions ≤4 cm Normal serum total bilirubin Normal albumin level Platelet count >50 × 10^9/mm^3 Prothrombin activity >50% Exclusion Portal vein thrombosis or extrahepatic metastases Objectives Elucidate incidence of local tumour recurrence after percutaneous MTA; evaluate risk factors	Percutaneous MTA (KY-2000, Kangyou Medical, Nanjing, China) 915 and 2450 MHz, 50–60 W Cooled shaft antennae	Outcomes Local tumour recurrence Statistical analysis Kaplan–Meier analysis Duration of follow-up Median 20.3 months, range 3–92.4 months	-

CCA = cholangiocarcinoma; CRC = colorectal cancer; HCC = hepatocellular carcinoma; MRI = magnetic resonance imaging; MTA = microwave thermal ablation; MTA = microwave tissue ablation; TACE = transcatheter arterial chemoembolisation; RFA = radiofrequency ablation; SD = standard deviation; SPSS = Statistical Package for Social Sciences

Table 63   Safety evidence profile table for MTA compared with RFA for patients with primary liver tumours (Population 1)

Outcome (units, follow-up)	*K* = no. of studies, study design *N* = no. of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance[a]
Adverse events (percutaneous ablation)	*K* = 2 SRs *K* = 1 RHCC, *N* = 879 *K* = 1 CS, *N* = 1136	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR = 0.63 (0.29, 1.38) (favouring RFA) OR = 1.63 (0.88, 3.03) (favouring RFA) MTA 3.1% vs RFA 3.5% events per total sessions; *P* = 0.041 (favouring MTA) MTA 2.6% of patients with event (no comparator)	Low ⊕⊕⊙⊙	Critical 8/9
Adverse events (surgical ablation)	*K* = 2 RHCC, *N* = 108	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	ORs between 0.35 (0.10, 1.20), *P* = 0.09, and 1.92 (0.47, 7.77), *P* = 0.36[a]	Very low ⊕⊙⊙⊙	Critical 8/9
Procedure related mortality (percutaneous ablation)	*K* = 1 RCCC, *N* = 879 *K* = 1 CS, *N* = 1136	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 1.16 (0.10, 12.87), *P* = 0.90[b] MTA 0.2% of patients with events (no comparator)	Low ⊕⊕⊙⊙	Critical 9/9
Procedure related mortality (surgical ablation)	*K* = 2 RHCC, *N* = 108	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 0% vs RFA 0% to 3% patients with events	Very low ⊕⊙⊙⊙	Critical 9/9

CS = case series; MTA = microwave tissue ablation; OR = odds ratio; RCCC = retrospective concurrent control cohort; RFA = radiofrequency ablation; RHCC = retrospective historical control cohort; SR = systematic review

[a] The importance of outcomes are measured on a scale of 1 to 9: 1-3 = not important; 4-6 = important; 7-9 = critical
[b] Odds ratio and *P* value were calculated by the authors of this assessment from the raw data provided in the study

Table 64 Effectiveness evidence profile table for MTA compared with RFA for patients with primary liver tumours (Population 1)

Outcome (units, follow-up)	K = no. of studies, study design N = no. of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results OR/HR/RR (95% CI)	Quality	Importance[a]
Local recurrence (percutaneous ablation)	K = 3 SRs K = 2 RHCC, N = 154	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	ORs between 1.01 (0.67, 1.50), P = 0.98, favouring MTA, and 1.17 (0.61, 2.24), P = 0.64 favouring RFA ORs between 1.13 (95% CI NR), P = 0.7, favouring RFA, and 2.17 (1.04, 4.50), P = 0.04, favouring MTA	Low ⊕⊕⊙⊙	Critical 8/9
Local recurrence—high tumour burden (percut ablation)	K = 1 SR, N = 266	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.46 (0.24, 0.89), P = 0.02, favouring MTA	Low ⊕⊕⊙⊙	Critical 8/9
Local recurrence (surgical ablation)	K = 2 RHCC, N = 108 K = 1 RCCC, N = 391	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 0%–23.1% vs RFA 9.1%–25.5% patients with events RR = 0.65 (95% CI NR), P = 0.32	Very low ⊕⊙⊙⊙	Critical 8/9
Local recurrence—very early stage HCC[a] (percutaneous ablation)	K = 1 SR, N = 143	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.48 (0.15, 1.57), P = 0.22, favouring RFA	Very low ⊕⊙⊙⊙	Critical 7/9
Local recurrence—early stage[a] (percut ablation)	K = 1 SR, N = 705	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.73 (0.45, 1.19), P = 0.21, favouring RFA	Very low ⊕⊙⊙⊙	Critical 7/9
Local recurrence—outside Milan criteria[a] (percut ablation)	K = 1 SR, N = 450	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 1.88 (1.10, 3.23), P = 0.02, favouring MTA	Low ⊕⊕⊙⊙	Critical 7/9
Complete ablation (percut	K = 3 SRs	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but	ORs between 1.12 (0.67, 6.07), P = 0.67, favouring MTA, and 0.98	Low	Critical 7/9

ablation)						no effect was observed	(0.85, 1.14), P = 0.82, favouring RFA	⊕⊕⊙⊙	
Complete ablation (surgical ablation)	K = 2 RHCC, N = 108	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 3.8%–7.7% vs RFA 0% to 6.4%	Very low ⊕⊙⊙⊙	Critical 9/9
OS y 1 (percutaneous ablation)	K = 2 SRs	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 1.11 (1.02, 2.23) OR 1.18 (0.46, 3.03)[b]	Low ⊕⊕⊙⊙	Critical 8/9
OS y 2 (percutaneous ablation)	K = 1 RHCC, N = 154	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	HR 1.59 (0.91, 2.77), P = 0.09, favouring MTA	Very low ⊕⊙⊙⊙	Critical 8/9
OS y 3 (percutaneous ablation)	K = 3 SRs	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.58 (0.32, 1.07) OR 0.76 (0.44, 1.32)[b]	Low ⊕⊕⊙⊙	Critical 8/9
OS y 6 (percutaneous ablation)	K = 1 SR, N = 449	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 1.51 (1.02, 2.23), P = 0.04	Very low ⊕⊙⊙⊙	Critical 8/9
OS y 1 (surgical ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 96.2% vs RFA 89.4%, P = 0.30	Very low ⊕⊙⊙⊙	Critical 8/9
OS y 3 (surgical ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 73.1% vs RFA 61.7%, P = 0.22	Very low ⊕⊙⊙⊙	Critical 8/9
OS y 5 (surgical ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 73.1% vs RFA 46.3%, P = 0.08	Very low ⊕⊙⊙⊙	Critical 8/9
Recurrence-free survival 1 y (percut ablation)	K = 1 SR, N = 668	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.79 (0.56, 1.13), P = 0.20	Low ⊕⊕⊙⊙	Critical 8/9
Recurrence-free survival 2 y (percut ablation)	K = 1 SR, N = 470	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.85 (0.58, 1.26), P = 0.42	Low ⊕⊕⊙⊙	Critical 8/9
Recurrence-free survival 3 y	K = 1 SR, N = 596	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but	OR 1.03 (0.73, 1.45), P = 0.99	Low ⊕⊕⊙⊙	Critical 8/9

(percut ablation)						no effect was observed			
Recurrence-free survival 4 y (percut ablation)	K = 1 SR, N = 596	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.72 (0.50, 1.04), P = 0.08	Low ⊕⊕⊙⊙	Critical 8/9
Recurrence-free survival 5 y (percut ablation)	K = 1 SR, N = 353	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	OR 0.60 (0.39, 0.94), P = 0.03	Very low ⊕⊙⊙⊙	Critical 8/9
Recurrence-free survival 1 y (surg ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 57.7% vs RFA 68.1%, P = 0.44	Very low ⊕⊙⊙⊙	Critical 7/9
Recurrence-free survival 3 y (surg ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 34.6% vs RFA 23.4%, P = 0.59	Very low ⊕⊙⊙⊙	Critical 7/9
Recurrence-free survival 5 y (surg ablation)	K = 1 RHCC, N = 73	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 13.8% vs RFA 14.6%, P = 0.74	Very low ⊕⊙⊙⊙	Critical 7/9
Ablation time (percutaneous ablation)	K = 1 SR K = 1 RCT, N = 72	Very serious	Not serious	Not serious	Serious	Confounding would suggest spurious effect, but no effect was observed	MTA 1–25 vs RFA 6–25 min per lesion MTA 33 ± 11 vs RFA 53 ± 16 min, P < 0.001	Very low ⊕⊙⊙⊙	Important 6/9
Ablation time (surgical ablation)	K = 1 RHCC, N = 35	Very serious	Not serious	Not serious	Serious	Confounding would suggest spurious effect, but no effect was observed	MTA 12 vs RFA 25 min per lesion	Very low ⊕⊙⊙⊙	Important 6/9
Number of sessions (percutaneous ablation)	K = 1 RCT, N = 72	Very serious	Not serious	Not serious	Not serious	None	WMD 1.3 (1.66, −0.94) sessions, favouring RFA	Very low ⊕⊙⊙⊙	Important 6/9
Hospital stay <1 day (surgical ablation)	K = 1 RHCC, N = 35	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 92% vs RFA 82% of patients	Very low ⊕⊙⊙⊙	Important 6/9

CI = confidence interval; HCC = hepatocellular carcinoma; HR = hazard ratio; MTA = microwave tissue ablation; RCCC = retrospective concurrent control cohort; RHCC = retrospective historical control cohort; NR = not reported; OR = odds ratio; OS = overall survival; RCT = randomised controlled trial; RFA = radiofrequency ablation; RR = relative risk; SR = systematic review; WMD = weighted mean difference

[a] Very early stage, single tumour ≤2 cm; early stage Milan criteria, single tumour ≤5 cm or up to 3 tumours ≤3 cm each; outside Milan criteria, single tumour >5 cm or > 3 nodules
[b] One SR (Chinnaratha, M. A. et al 2016) appeared to report the inverse of survival (ie, the number of deaths); therefore, the OR is not strictly comparable to other studies

Table 65   Effectiveness evidence profile table for MTA compared with RFA for patients with secondary liver tumours (Population 2)

Outcome (units, follow-up)	*K* = no. of studies, study design *N* = no. of patients	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
Local tumour recurrence	*K* = 1 RCCC, *N* = 89	Serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 8.6% vs RFA 20.3% of patients with events, *P* = 0.07	Low ⊕⊕⊙⊙	Critical 8/9
Distant tumour recurrence	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 42.9% vs RFA 55.6% patients with events, *P* = 0.24	Low ⊕⊕⊙⊙	Important 5/9
OS all years	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	*P* = 0.43	Low ⊕⊕⊙⊙	Critical 8/9
OS 1 y	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 82.4 vs RFA 86.6% patients	Low ⊕⊕⊙⊙	Critical 8/9
OS 2 y	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 66.9% vs RFA 54.8% patients	Low ⊕⊕⊙⊙	Critical 8/9
OS 3 y	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 55.8% vs RFA 44.3% patients	Low ⊕⊕⊙⊙	Critical 8/9
OS 5 y	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 44.0% vs RFA 31.7% patients	Low ⊕⊕⊙⊙	Critical 8/9
Complete ablation	*K* = 1 RCCC, *N* = 89	Very serious	Not serious	Not serious	Not serious	Confounding would suggest spurious effect, but no effect was observed	MTA 93.5% vs RFA 84.3% patients, *P* = 0.094	Low ⊕⊕⊙⊙	Critical 8/9

MTA = microwave tissue ablation; OS = overall survival; RCCC = retrospective concurrent control cohort; RFA = radiofrequency ablation; RHCC = retrospective historical control cohort

APPENDIX F   EXCLUDED STUDIES

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APPENDIX G NHMRC DIMENSIONS OF EVIDENCE AND EVIDENCE HIERARCHY

Dimensions of evidence (NHMRC 2000)

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design (see following table for applicable study designs)
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The *P*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

Designations of level of evidence according to interventional type research question (including explanatory notes) (Merlin, Weston & Tooher 2009)

Level	Intervention[1]
I[2]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (ie, alternative allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[3] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single-arm studies[4] ▪ Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Explanatory notes

[1] Definitions of these study designs are provided on pages 7–8 of *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000) and in the accompanying glossary.

[2] A systematic review will be assigned a level of evidence only as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower-level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should cover at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

³   This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie, use A vs B and B vs C to determine A vs C, with statistical adjustment for B).

⁴   Comparing single-arm studies; ie, case series from two studies. This would also include unadjusted indirect comparisons (ie, use A vs B and B vs C to determine A vs C, where there is no statistical adjustment for B).

Note A: Comparative harms and safety should be assessed according to the hierarchy presented for each of the research questions, strictly within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false-positive and false-negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question; eg, level II intervention evidence, level IV diagnostic evidence, level III-2 prognostic evidence.

Note C: Each study that is attributed a 'level of evidence' should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

Source: Hierarchies adapted and modified from (Bandolier 1999; NHMRC 1999; Phillips et al 2001)

³   This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie,

APPENDIX H ADDITIONAL INFORMATION FOR ECONOMIC ANALYSIS

SEARCH STRATEGIES

Table 66   Search strategies used in the literature search

Search	Search query for economic evaluations	PubMed	EMBASE
#1	(liver OR liver[MeSH] OR hepat*) AND (tumour OR tumor OR tumor[MeSH] OR lesion OR neoplasm OR neoplasm[MeSH] OR cancer OR carcino* OR onco*)	310,165	81,302
#2	microwave OR microwaves[MeSH] OR MTA OR MWA OR radiofrequency OR 'radio frequency' OR electrocoag* OR radio waves[MeSH] OR short-wave therapy[MeSH] OR 'radio waves' OR 'short-wave therapy'	79,024	16,811
#3	('economics'[MeSH Terms] OR 'costs and cost analysis'[MeSH Terms] OR 'cost allocation'[MeSH Terms] OR 'cost benefit analysis'[MeSH Terms] OR 'cost control'[MeSH Terms] OR 'cost savings'[MeSH Terms] OR 'cost of illness'[MeSH Terms] OR 'health care costs'[MeSH Terms] OR 'drug costs'[MeSH Terms] OR 'health expenditures'[MeSH Terms] OR 'economics, medical'[MeSH Terms] OR 'economics, pharmaceutical'[MeSH Terms] OR 'fees and charges'[MeSH Terms] OR 'budgets'[MeSH Terms] OR 'high cost'[All Fields] OR 'low cost'[All Fields] OR 'cost utility'[All Fields] OR 'economics'[All Fields] OR 'financial'[All Fields] OR finance[All Fields]) OR ('healthcare cost'[All Fields] OR 'health care cost'[All Fields]) OR 'cost estimate'[All Fields] OR 'unit cost'[All Fields] OR ('economics, pharmaceutical'[MeSH Terms] OR ('economics'[All Fields] AND 'pharmaceutical'[All Fields]) OR 'pharmaceutical economics'[All Fields] OR 'pharmacoeconomic'[All Fields]) OR ('commerce'[MeSH Terms] OR 'commerce'[All Fields] OR 'price'[All Fields]) OR ('costs'[All Fields] AND 'cost'[All Fields] AND 'analysis'[All Fields]) OR 'costs and cost analysis'[All Fields] OR 'pricing'[All Fields])) OR (cost-effectiveness OR 'cost effectiveness' OR 'economic evaluation')	818,741	98,004
#4	(#1 AND #2 AND #3)	70	116

ADDITIONAL ANALYSIS USING PRIVATE SECTOR COSTS

POPULATION 1

Results

Table 67 shows the overall costs and the incremental cost per patient calculated for the intervention and comparator, using costs from the NHCDC cost report for private hospitals, Round 13 (2008–09) (Department of Health 2012) with adjustment for inflation[10].

Table 67   Costs associated with MTA and RFA, Population 1

Item description	MTA	RFA
Ablation procedure	$817	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Other hospital costs[1]	$5,003	$5,003
Total	**$6,002**	**$6,002**
Incremental cost per patient	-	**$0**

[1] The average cost of AR-DRG H05B excluding the costs associated with medical and imaging services

Source: Table 28 and (Department of Health 2012)

MTA = microwave tissue ablation; RFA = radiofrequency ablation

Sensitivity analysis

Sensitivity analyses presented in Table 68 assess the impact of varying costs associated with the MTA procedures, reduction in hospital and anaesthetic costs with MTA, and number of sessions required per patient for MTA and RFA.

Table 68   Sensitivity analyses of key parameters, Population 1

Sensitivity analyses	MTA	RFA	Incremental cost per patient
Base case	**$6,002**	**$6,002**	**$0**
Weighted MBS fee for MTA: $962[1]	$6,146	$6,002	$145
Reducing hospital costs of MTA by 10%	$5,501	$6,002	−$501
Reducing hospital costs of MTA by 20%	$5,001	$6,002	−$1,001
Reducing 1 basic unit of anaesthesia for MTA	$5,982	$6,002	−$20
Reducing 2 basic units of anaesthesia for MTA	$5,962	$6,002	−$40
Number of MTA sessions required per patient: 2	$12,003	$6,002	$6,002
Number of RFA sessions required per patient: 1.2	$6,002	$7,202	−$1,200

[1] Cost implications of weighted MBS fee based on ≤3 or >3 lesions treated

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cells indicate potential cost-savings (negative value for incremental cost) with MTA

Results

Table 69 shows the overall costs and the incremental cost per patient calculated for the intervention and comparator, using 2008–09 costs from NHCDC cost report for private hospitals (Department of Health 2012) with adjustment for inflation[10].

Table 69   Costs associated with MTA and RFA, Population 2

Item description	MTA	RFA
Ablation procedure	$817	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Chemotherapy	$539	$539
Other hospital costs[1]	$5,003	$5,003
Total	**$6,287**	**$6,287**
Incremental cost per patient	-	**$0**

[1] Average cost of AR-DRG H05B from private sector cost report

Source: Table 28 and (Department of Health 2012)

MTA = microwave tissue ablation; RFA = radiofrequency ablation

Sensitivity analysis

Sensitivity analyses presented in Table 70 assess the impact of varying costs associated with the MTA procedures, reduction in hospital and anaesthetic costs with MTA, number of sessions required per patient for MTA and RFA, and 10 per cent reduction in chemotherapy usage with MTA.

Table 70   Sensitivity analyses of key parameters, Population 2

Sensitivity analyses	MTA	RFA	Incremental cost per patient
Base case	$6,287	$6,287	$0
Weighted MBS fee for MTA: $1,107	$6,577	$6,287	$290
Reducing hospital costs of MTA by 10%	$5,787	$6,287	−$501
Reducing hospital costs of MTA by 20%	$5,286	$6,287	−$1,001
Reducing 1 basic unit of anaesthesia for MTA	$6,267	$6,287	−$20
Reducing 2 basic units of anaesthesia for MTA	$6,247	$6,287	−$40
Number of MTA sessions required per patient: 2	$12,575	$6,287	$6,287
Number of RFA sessions required per patient: 1.2	$6,287	$7,545	−$1,257
Number of RFA sessions required per patient: 2	$6,287	$12,575	−$6,287
Relative reduction of 10% in chemotherapy usage with MTA	$6,233	$6,287	−$54

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cells show potential cost-savings (negative value for incremental cost) with MTA

APPENDIX I ECONOMIC ANALYSES BASED ON THE PROPOSED GRADUATED FEE FOR MTA

INPUTS TO THE ECONOMIC EVALUATION

STRATIFICATION OF PATIENTS BY NUMBER OF LESIONS

The applicant proposed graduated fees for MTA based on the number of lesions treated ($1300 for ablation of 2–3 lesions, $1600 for ablation of 4–5 lesions and $2000 for ablation of >5 lesions). PASC advised that graduated fees for up to 5 lesions should be considered in the assessment (MSAC 2016).

Few studies provided the required stratification of patients by the number of lesions (Table 71). Only 1 study reported the number of patients with more than 3 lesions. The applicability and generalisability of these studies in the Australian context are questionable as the studies are not limited to the proposed target population and may have inherent selection bias.

Table 71 Studies providing data on patients with number of lesions

Study	Hepatic lesion	N	Proportion of patients with '*n*' lesions
Babawale et al (2015)	Metastases	49	≤3: 82% 4–7: 16% 8: 2%
Abdelaziz et al (2014)	HCC	111	1: 87% 2: 12% 3: 2%
Chinnaratha et al (2016)	HCC	126	Single: 86% Multiple: 14%
Liu et al (2013b)	HCC	80	Single: 65% Multiple: 35%
Liang et al (2009a)	HCC/metastases	1007	Single: 75% Multiple: 25%

HCC = hepatocellular carcinoma; *N* = number of patients

The clinical experts suggested that approximately 70 per cent of HCC patients are treated for up to 3 lesions; in contrast, nearly 60 per cent of patients with secondary liver metastasis have more than 5 lesions being treated.[13] The stratifications suggested by clinicians by the number of lesions per patient for populations 1 and 2 are summarised in Table 72.

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[13] Email communication with the clinical expert panel; responses received on 18 and 19 July 2016.

Table 72   Stratification of the target populations on the basis of number of lesions per patient

Number of lesions	Population 1	Population 2
1–3	70%	20%
4–5	15%	20%
>5	15%	60%

COST OF PROCEDURE

The cost of RFA is based on the current MBS fees for items 50950 and 50952, $817. A weighted cost of MTA is based on the proposed graduated fees (MSAC 2016) and the suggested stratification of Populations 1 and 2 by the number of lesions treated per patients (Table 72).

Table 73 summarises the weighted cost of MTA and the cost of RFA used in the analysis.

Table 73   Weighted cost of MTA based on the number of lesions treated per patient

Number of lesions	Proposed fee	Population 1	Population 2
1–3	$1,300	70% of proposed fee	20% of proposed fee
4–5	$1,600	15% of proposed fee	20% of proposed fee
>5	$2,000	15% of proposed fee	60% of proposed fee
Weighted cost	-	**$1,450**	**$1,780**

MTA = microwave tissue ablation

All other inputs used in the analyses are the same as discussed in Section D.4.

POPULATION 1

RESULTS OF THE ECONOMIC EVALUATION

When only the procedural costs of MTA and RFA are compared (excluding all other associated anaesthetic and other healthcare costs), the proposed graduated fee for MTA is estimated to result in an incremental cost of $633 per patient (Table 74).

Table 74   Incremental cost of MTA excluding other associated costs, Population 1

Item description	MTA	RFA	Incremental cost
Ablation procedure	$1,450	$817	**$633**

MTA = microwave tissue ablation; RFA = radiofrequency ablation

When all other associated healthcare costs are included in the analysis, the cost is estimated to be $7,868 for MTA and $7,235 for RFA. However, since the other costs are considered to be similar across the two procedures, the incremental cost remains the same ($633).

Table 75 shows the overall costs and the incremental cost per patient calculated for the intervention and comparator, with the base-case assumptions.

Table 75 Costs associated with MTA and RFA, Population 1

Item description	MTA	RFA
Ablation procedure	$1,450	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Other hospital costs	$6,236	$6,236
Total	**$7,868**	**$7,235**
Incremental cost per patient	-	**$633**

Source: Table 28 and Table 73

MTA = microwave tissue ablation; RFA = radiofrequency ablation

SENSITIVITY ANALYSES

Table 76 presents the sensitivity analyses of key parameters discussed in Section D.6.a.

Table 76 Sensitivity analyses of key parameters, Population 1

Sensitivity analyses	MTA	RFA	Incremental cost per patient	Change from base case (%)
Base case	**$7,868**	**$7,235**	**$633**	-
MBS fee for MTA: $817	$7,235	$7,235	$0	−100
Reducing hospital costs of MTA by 10%	$7,244	$7,235	$9	−99
Reducing hospital costs of MTA by 20%	$6,621	$7,235	−$614	−197
Reducing 1 basic unit of anaesthesia for MTA	$7,848	$7,235	$613	−3
Reducing 2 basic units of anaesthesia for MTA	$7,828	$7,235	$593	−6
Number of MTA sessions required per patient: 2.4	$18,883	$7,235	$11,648	+1740
Number of RFA sessions required per patient: 1.2	$7,868	$8,682	−$814	−229

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cells indicate potential cost-savings (negative value for incremental cost) with MTA

As shown in Table 76, the MBS fee for MTA, hospital costs and the number of sessions required for either procedure are the key drivers of the economic analysis. If treatment with MTA results in reduction of associated hospital costs by 10 per cent or more, it may reduce costs.

POPULATION 2

RESULTS OF THE ECONOMIC EVALUATION

When only the procedural costs of MTA and RFA are compared (excluding all other associated anaesthetic and other healthcare costs), the proposed graduated fee for MTA is estimated to result in an incremental cost of $963 per patient (Table 77).

Table 77 Incremental cost of MTA excluding other associated costs, Population 2

Item description	MTA	RFA	Incremental cost
Ablation procedure	$1,450	$817	**$963**

MTA = microwave tissue ablation; RFA = radiofrequency ablation

When all other associated healthcare costs are included in the analysis, the cost is estimated to be $9,003 for MTA and $8,040 for RFA. However, since the other costs are considered to be similar across the two procedures, the incremental cost remains the same ($963).

Table 78 shows the overall costs and the incremental cost per patient calculated for the intervention and comparator, with the base-case assumptions.

Table 78   Costs associated with MTA and RFA, Population 2

Item description	MTA	RFA
Ablation procedure	$1,780	$817
Pre-anaesthesia consultation	$43	$43
Initiation of management of anaesthesia	$139	$139
Chemotherapy	$805	$805
Other hospital costs	$6,236	$6,236
Total	**$9,003**	**$8,040**
Incremental cost per patient	-	**$963**

Source: Table 28 and Table 73

MTA = microwave tissue ablation; RFA = radiofrequency ablation

SENSITIVITY ANALYSES

Sensitivity analyses presented in Table 79 assesses the impact of varying costs associated with the procedures: MBS fees charged, hospital costs, anaesthesia cost, chemotherapy usage and number of ablation sessions required, as discussed in Section D.6.b.

Table 79   Sensitivity analyses of key parameters, Population 2

Sensitivity analyses	MTA	RFA	Incremental cost per patient	Change from base case (%)
Base case	**$9,003**	**$8,040**	**$963**	-
MBS fee for MTA: $817	$8,040	$8,040	$0	−100
MBS fee for MTA: $1,300	$8,523	$8,040	$483	−50
Reducing hospital costs of MTA by 10%	$8,379	$8,040	$339	−65
Reducing hospital costs of MTA by 20%	$7,755	$8,040	−$284	−130
Reducing 1 basic unit of anaesthesia for MTA	$8,982	$8,040	$943	−2
Reducing 2 basic units of anaesthesia for MTA	$8,963	$8,040	$923	−4
Number of MTA sessions required per patient: 2.4	$21,606	$8,040	$13,567	+1309
Number of RFA sessions required per patient: 1.2	$9,003	$9,647	−$645	−167
Number of RFA sessions required per patient: 2	$9,003	$16,079	−$7,077	−835
Relative reduction of 10% in chemotherapy usage with MTA	$8,851	$8,040	$811	+16

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation; RFA = radiofrequency ablation

Shaded cell indicate potential cost-savings (negative value for incremental cost) with MTA

As shown in Table 79, the MBS fee for MTA, hospital costs and the number of sessions required for either procedure are the key drivers of the economic analysis.

APPENDIX J   ADDITIONAL INFORMATION FOR FINANCIAL ANALYSIS

PROJECTED INCIDENCE RATES OF PRIMARY LIVER CANCER AND COLORECTAL CANCER

Table 80   Incidence of liver and colorectal cancer (1982–2022)

Year	Incidence of liver cancer in Australia (per 100,000)	Incidence of CRC in Australia (per 100,000)	Source / explanation
1982	1.8	58.2	AIHW ACIM books 2016a, b
1983	1.6	58.2	-
1984	1.7	59.1	-
1985	1.7	61.7	-
1986	2.1	60.2	-
1987	2.2	60.3	-
1988	2.1	59.0	-
1989	2.3	61.2	-
1990	2.3	60.5	-
1991	2.5	63.9	-
1992	2.8	63.1	-
1993	3.1	62.8	-
1994	3.2	64.0	-
1995	3.1	64.0	-
1996	3.3	64.6	-
1997	3.5	64.4	-
1998	3.5	62.9	-
1999	3.9	64.2	-
2000	4.2	65.8	-
2001	4.6	66.2	-
2002	4.6	63.5	-
2003	4.6	62.7	-
2004	5.0	63.4	-
2005	5.3	62.4	-
2006	5.6	63.7	-
2007	5.5	64.8	-
2008	6.1	62.8	-
2009	6.1	61.3	-
2010	6.3	62.4	-
2011	6.2	61.7	-
2012	6.4	59.0	-
2013	6.6	62.0	Linear equation in Figure 8
2014	6.7	62.0	$y = 0.173x + 1.0198$ (for liver cancer)

Year	Incidence of liver cancer in Australia (per 100,000)	Incidence of CRC in Australia (per 100,000)	Source / explanation
2015	6.9	62.0	Average incidence rate for CRC
2016	7.1	62.0	-
2017	7.2	62.0	-
2018	7.4	62.0	-
2019	7.6	62.0	-
2020	7.8	62.0	-
2021	7.9	62.0	-
2022	8.1	62.0	-

ACIM = Australian Cancer Incidence and Mortality; AIHW = Australian Institute of Health and Welfare; CRC = colorectal cancer

Source: (Australian Institute of Health and Welfare 2016a, 2016b)
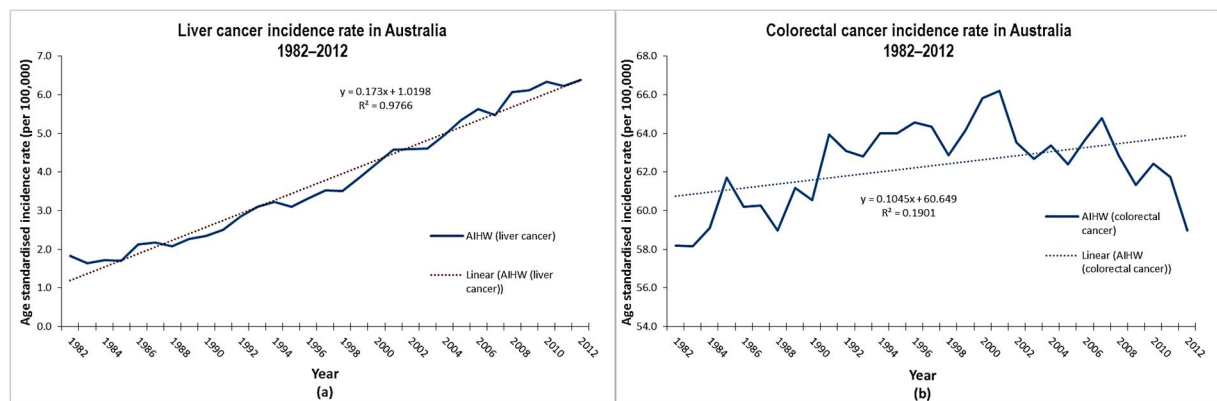
Figure 8   **Age-standardised incidence rates for liver and colorectal cancer**

Source: (Australian Institute of Health and Welfare 2016a, 2016b)

Data in Table 80 were projected over the next 10 years (2013–2022) on the assumption of a linear increase in the incidence of liver cancer (R^2 = 0.98; Figure 8a). The trend in the incidence of colorectal cancer could not be extrapolated (Figure 8b).

NUMBER OF AUSTRALIAN HOSPITAL PROCEDURES FOR THE DESTRUCTION OF LIVER TISSUE

Although RFA is listed only for primary HCC, and MTA not listed for any of the proposed indications, both services are currently being used in Australian hospitals. The number of liver ablations performed in public and private hospitals in Australia were extracted from the national database (AIHW National Hospital Morbidity Database 2015) and are summarised in Table 81. It is assumed that 'other destruction of liver' represents the number of microwave ablations performed, as these are not assigned an MBS item number. It is not possible to estimate the stratification of these procedures on the basis of the type of liver cancer.

Table 81   Number of Australian hospital procedures for the destruction of liver tissue, 2011–14

Row	Procedure	2011–12	2012–13	2013–14
A	50950-00 Radiofrequency ablation of liver[a]	359	325	311
B	90299-00 Other destruction of liver[a]	44	72	107
C	**Total (= A + B)**	**403**	**397**	**418**

[a] From Chapter 7, 'Procedures on digestive system', subchapter 'Procedures 956 Other procedures on liver', Block 951–56 Liver

Since RFA currently has a narrower MBS listing (primary unresectable HCC only), and MTA is not listed for any of the proposed indications, most ablations are performed in public hospitals. Neo et al analysed the records of 1544 patients registered on the South Australian Clinical Registry for Metastatic Colorectal Cancer to reveal the patterns of practice and survival estimates for CRC in South Australia (Neo et al 2011). Only 9 RFAs were performed in 945 patients (1 per cent) with liver as the site of metastases. That study is based on data collected up to 2010 and may not reflect the role of ablative therapies in current clinical practice, as MTA was approved by the Therapeutic Goods Administration in Australia in 2010.

APPENDIX K FINANCIAL ANALYSES BASED ON THE PROPOSED GRADUATED FEE FOR MTA

For this analysis, all estimates of cost to MBS and co-payments for MTA are calculated for the proposed categories (based on number of lesions; see Table 72, Appendix I) and then weighted according to the proportion of patients estimated in each category.

POPULATION 1

ESTIMATED USE AND COSTS OF MTA

Table 82 summarises all the steps taken to estimate the weighted average cost of MTA (to MBS and co-payment) per service.

Table 82   Estimated cost per MTA procedure

Row	Description	Up to 3 lesions	4–5 lesions	>5 lesions
A	Proportion of patients with '*n*' lesions[1]	70%	15%	15%
B	Proposed fee	$1,300	$1,600	$2,000
C	Benefit paid (inpatient services: 75% × B)	$975	$1,200	$1,500
D	Benefit paid (outpatient services: 85% × B)	$1,105	$1,360	$1,700
-	*Percutaneous MTAs (93%)*	-	-	-
E	Weighted cost to MBS (60% inpatient and 40% outpatient) per service (= 60% × C + 40% × D)	$1,027	$1,264	$1,580
F	*Weighted benefit paid per service (all categories)[2]*	-	-	**$1,146**
G	Average co-payment per service	$195	$240	$300
H	*Weighted co-payment (all categories)[2]*	-	-	**$218**
I	**Total cost per percutaneous MTA (= F+ H)**	-	-	**$1,363**
-	*Intraoperative MTAs (7%)*	-	-	-
J	Average benefit paid per service (100% inpatient)	$975	$1,200	$1,500
K	*Weighted benefit paid per service (all categories)[2]*	-	-	**$1,088**
L	Average co-payment per service	$325	$400	$500
M	*Weighted co-payment (all categories)[2]*	-	-	**$363**
N	**Total cost per intraoperative MTA (= K + M)**	-	-	**$1,450**

[1] See Table 72, Appendix I

[2] Calculated as sum of values in the row above multiplied by proportion in row A

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

The estimated costs of MTA per service, weighted across all subgroups of patients for Population 1, are an average MBS cost of $1,141/service and an average co-payment of $228/service.

Table 83 and Table 84 summarise the costs of MTA services to MBS and private sector.

Table 83   Estimated cost of MTA services to MBS

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
O	Number of percutaneous services[1]	121	134	149	164	180
P	Total MBS cost of percutaneous MTA at $1,146/service (= O × F)	$138,228	$153,888	$170,454	$187,950	$206,384
Q	Number of intraoperative services[1]	8	9	10	11	13
R	Total MBS cost of intraoperative MTA at $1022/service (= Q × K)	$9,186	$10,227	$11,328	$12,490	$13,715
S	**Total cost of MTA to MBS**	**$147,414**	**$164,115**	**$181,782**	**$200,440**	**$220,100**

[1] Source: Table 38

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 84   Estimated cost of MTA services to private sector (co-payments)

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
O	Number of percutaneous services[1]	121	134	149	164	180
T	Total co-payments of percutaneous MTA (= O × H)	$26,246	$29,219	$32,365	$35,687	$39,187
Q	Number of intraoperative services[1]	8	9	10	11	13
U	Total co-payments for intraoperative MTAs (= Q × M)	$3,062	$3,409	$3,776	$4,163	$4,572
V	**Total cost of MTA to private sector**	**$29,308**	**$32,628**	**$36,141**	**$39,850**	**$43,759**

[1] Source: Table 38

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

ESTIMATED COSTS OFFSET

Estimated costs per RFA service to the MBS ($659 for percutaneous and $592 intraoperative RFA) and to the private sector ($94 and $512, respectively) are presented in Table 39. Estimates of the number of comparator services offset by MTA are presented in Table 43. (See Section E.3.a.) The costs offset by comparator services are presented in Table 44.

FINANCIAL IMPLICATIONS FOR THE MBS

Table 85 summarises the financial implications to the MBS over the next 5 years resulting from the proposed listing of MTA.

Table 85   Total costs to the MBS associated with MTA

-	2017–18	2018–19	2019–20	2020–21	2021–22
MTA	-	-	-	-	-
Number of MBS services	130	144	160	176	194
Cost to the MBS	$147,414	$164,115	$181,782	$200,440	$220,100
MBS services offset	-	-	-	-	-
Number of MBS services offset	121	126	131	137	142
Costs offset	$79,376	$82,648	$85,980	$89,371	$92,818
Net cost to the MBS	**$68,038**	**$81,467**	**$95,802**	**$111,069**	**$127,282**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

FINANCIAL IMPLICATIONS FOR OTHER HEALTH BUDGETS

Table 86 summarises the financial implications to the private sector (patients, PHIs) of listing MTA, calculated as the sum of co-payments and hospital costs associated with the procedures.

Table 86   Total costs to private sector associated with MTA listing for Population 1

-	2017–18	2018–19	2019–20	2020–21	2021–22
Number of MTA services	130	144	160	176	194
Cost to private sector	$838,446	$933,439	$1,033,924	$1,140,047	$1,251,865
Offsets	-	-	-	-	-
Number of services offset	121	126	131	137	142
Costs offset	$770,986	$802,774	$835,134	$868,077	$901,550
Net costs to private sector*	**$67,460**	**$130,664**	**$198,790**	**$271,970**	**$350,315**

* Including co-payments and hospital costs

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Table 87 presents a sensitivity analysis around inputs to the financial model.

Table 87   Sensitivity analysis of financial implications of listing MTA for Population 1

-	2017–18	2018–19	2019–20	2020–21	2021–22
Base case	-	-	-	-	-
Net cost of MTA to the MBS	**$68,038**	**$81,467**	**$95,802**	**$111,069**	**$127,282**
Net cost of MTA to the private sector[1]	**$14,348**	**$17,052**	**$19,936**	**$23,007**	**$26,266**
Proportion of patients eligible for ablation: 20% (base case: 25%)	-	-	-	-	-
Net cost of MTA to the MBS	$54,430	$65,612	$76,642	$88,855	$101,826
Net cost of MTA to the private sector	$11,478	$13,729	$15,949	$18,405	$21,013
Assuming no extension of services in private sector (base case 2%–10%)	-	-	-	-	-
Net cost of MTA to the MBS	$58,362	$60,768	$63,218	$65,711	$68,245
Net cost of MTA to the private sector	$12,424	$12,937	$13,458	$13,989	$14,528
Assuming all services as inpatient (base case: 60%)	-	-	-	-	-
Net cost of MTA to the MBS	$61,039	$73,675	$87,172	$101,552	$116,832
Net cost of MTA to the private sector	$31,845	$36,531	$41,513	$46,798	$52,390
Assuming 80% services as inpatient (base case: 60%)	-	-	-	-	-
Net cost of MTA to the MBS	$64,539	$77,571	$91,487	$106,311	$122,057
Net cost of MTA to the private sector	$23,097	$26,792	$30,725	$34,902	$39,328

[1] Net costs to private sector in this table represent co-payments only and exclude all other hospital costs

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

POPULATION 2

ESTIMATED USE AND COSTS OF MTA

All inputs included in the analysis are the same as used in Section E.2.b, but the costs to the MBS and co-payments associated with MTA services are included here. Table 88 presents the estimates for costs associated with MTA services weighted by the number of lesions.

Table 88   Estimated cost of per MTA procedure

Row	Description	Up to 3 lesions	4–5 lesions	>5 lesions
A	Proportion of patients with 'n' lesions[1]	20%	20%	60%
B	Proposed fee	$1,300	$1,600	$2,000
C	Benefit paid (= 75% × B)	$975	$1,200	$1,500
D	**Weighted benefit paid per service[2]**	-	-	**$1,335**
E	Co-payment per service (= 25% × B)	$325	$400	$500
F	**Weighted co-payment per service[3]**	-	-	**$445**

[1] Source: Table 73

[2] Calculated as sum of product of rows A and C. [3] Calculated as sum of product of rows A and E

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

Table 89 provides the estimated costs of MTA services to the MBS over the first 5 years of listing.

Table 89   Estimated cost of MTA services to MBS and private sector (co-payments)

Row	Description	2017–18	2018–19	2019–20	2020–21	2021–22
G	Estimated number of MBS-funded MTA services	45	48	52	57	61
H	**Total cost of MTA to MBS (= D × G)**	**$59,483**	**$64,663**	**$69,978**	**$75,429**	**$81,009**
I	**Total cost of MTA to private sector (= F × G)**	**$19,828**	**$21,554**	**$23,326**	**$25,143**	**$27,003**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

As RFA is not currently MBS listed for Population 2, it is assumed that there are no costs offsets in the private sector.

FINANCIAL IMPLICATIONS FOR THE MBS

Table 90 summarises the financial implications to the MBS over the next 5 years resulting from the proposed listing of MTA.

Table 90   Total costs to the MBS associated with MTA

-	2017–18	2018–19	2019–20	2020–21	2021–22
MTA	-	-	-	-	-
Number of MBS services	45	48	52	57	61
Cost to the MBS	**$59,483**	**$64,663**	**$69,978**	**$75,429**	**$81,009**

-	2017–18	2018–19	2019–20	2020–21	2021–22
MBS services offset	-	-	-	-	-
Number of MBS services offset	0	0	0	0	0
Costs offset	$0	$0	$0	$0	$0
Net cost to the MBS	**$59,483**	**$64,663**	**$69,978**	**$75,429**	**$81,009**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

FINANCIAL IMPLICATIONS FOR OTHER HEALTH BUDGETS

Table 91 summarises the financial implications to private sector (patients, PHIs) of listing MTA, including co-payments and hospital costs associated with MTA services.

Table 91   Total costs to private sector associated with MTA listing for Population 2

-	2017–18	2018–19	2019–20	2020–21	2021–22
Number of MTA services	45	48	52	57	61
Number of services offset	0	0	0	0	0
Net costs to private sector (including co-payments)	**$286,956**	**$311,947**	**$337,588**	**$363,882**	**$390,804**

MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

Table 92 presents a sensitivity analysis around inputs to the financial model.

Table 92   Sensitivity analysis of financial implications of listing MTA for Population 2

-	2017–18	2018–19	2019–20	2020–21	2021–22
Base case	-	-	-	-	-
Net cost of MTA to the MBS	**$59,483**	**$64,663**	**$69,978**	**$75,429**	**$81,009**
Net cost of MTA to the private sector[1]	**$19,828**	**$21,554**	**$23,326**	**$25,143**	**$27,003**
Proportion of patients eligible for ablation: 1% (base case: 5%)	-	-	-	-	-
Net cost of MTA to the MBS	$11,897	$12,933	$13,996	$15,086	$16,202
Net cost of MTA to the private sector	$3,966	$4,311	$4,665	$5,029	$5,401
Proportion of patients eligible for ablation: 10% (base case: 5%)	-	-	-	-	-
Net cost of MTA to the MBS	$118,966	$129,327	$139,957	$150,858	$162,019
Net cost of MTA to the private sector	$39,655	$43,109	$46,652	$50,286	$54,006
Proportion of CRC patients with CRLM: 25% (base case 20%)	-	-	-	-	-
Net cost of MTA to the MBS	$74,354	$80,829	$87,473	$94,286	$101,262
Net cost of MTA to the private sector	$24,785	$26,943	$29,158	$31,429	$33,754
Assuming 10% of services in private sector (base case 29%–37%)	-	-	-	-	-
Net cost of MTA to the MBS	$20,511	$20,859	$21,206	$21,551	$21,894
Net cost of MTA to the private sector	$6,837	$6,953	$7,069	$7,184	$7,298

-	2017–18	2018–19	2019–20	2020–21	2021–22
Assuming 20% of services in private sector (base case 29%–37%)	-	-	-	-	-
Net cost of MTA to the MBS	$41,023	$41,718	$42,411	$43,102	$43,789
Net cost of MTA to the private sector	$13,674	$13,906	$14,137	$14,367	$14,596
Assuming 30% of services in private sector (base case 29%–37%)	-	-	-	-	-
Net cost of MTA to the MBS	$61,534	$62,577	$63,617	$64,653	$65,683
Net cost of MTA to the private sector	$20,511	$20,859	$21,206	$21,551	$21,894

[1] Net costs to private sector in this table represent co-payments only and exclude all other hospital costs.

CRC = colorectal cancer; CRLM = colorectal liver metastases; MBS = Medicare Benefits Schedule; MTA = microwave tissue ablation

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